Author:
Bibby, Anna C

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A Trial of Intra-pleural bacteriaL immunoTherapy in mesothelioma (TILT) – a feasibility study using the trial within a cohort methodology

Anna Claire Bibby

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Academic Respiratory Unit, Translational Health Sciences, Bristol Medical School

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ABSTRACT

Introduction

Malignant pleural mesothelioma (MPM) is an incurable, asbestos-related cancer of the chest cavity. Treatment options are limited, although immunotherapy has shown promise in recent trials. This research explored bacterial immunotherapy in MPM, specifically the feasibility and acceptability of a trial of intra-pleural bacterial agents, using an innovative, pragmatic trial design.

Methods

Mixed methods were used. The existing literature on intra-pleural bacterial agents in pleural malignancy was summarised. Subsequently, a population-based cohort study was undertaken to examine whether bacteria in the pleural space due to infection were associated with survival in mesothelioma. This was followed by a feasibility study of two intra-pleural bacterial agents in MPM, using the trial within a cohort (TwiC) methodology. Qualitative interviews with participants and their relatives were used to explore experiences of MPM and trial participation.

Results

Previous studies of intra-pleural bacterial agents were methodologically heterogenous and at risk of bias, rendering data synthesis impossible. In contrast to the original hypothesis, pleural infection was associated with shorter survival in mesothelioma, although confounding could have affected this finding.

The trial did not meet the pre-specified recruitment criteria and was therefore deemed unfeasible. Additionally, it was not possible to maintain blinding of control participants and post-randomisation attrition was problematic. Bacterial agents generated significant inflammatory responses but, despite this, the trial processes and methodology were generally acceptable to participants and relatives.

Qualitative interviews revealed that MPM patients sought certainty and absolutes in response to anxiety about their future. This affected their perception of risk and created challenges in communicating uncertainty.

Discussion

The efficacy of intra-pleural bacterial immunotherapy in MPM remains unproven, but future trials should not employ the TwiC design. Given the importance of quality of life to people with MPM, effective communication about potential side effects and risks of treatment is crucial.

AUTHOR'S DECLARATION

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Research Degree Programmes and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

SIGNED:  **DATE:** 01/08/2020

PUBLICATIONS ARISING FROM THIS THESIS

1. Bibby AC, de Fonseka D, Carslake DJ & Maskell NA. Is pleural infection associated with longer survival in mesothelioma? A population-based cohort study using data from Hospital Episode Statistics. *Cancer Epidemiology* 2019; 59:75-82.

2. Bibby AC & Maskell N. Checkpoint inhibitors in mesothelioma: hope for the future? *Lancet Oncol*. 2019;20(2): 172-174.

3. Bibby AC, Halford P, De Fonseka D, Morley AJ, Smith S, Maskell NA. The prevalence and clinical relevance of non-expandable lung in malignant pleural mesothelioma. A prospective, single-center cohort study of 229 patients. *Annals of the American Thoracic Society* 2019;16(10): 1273-1279.

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Authors' contributions to each project were confirmed at publication. Specific author contributions are described at the beginning of each relevant chapter in this thesis.

Signed & dated:

Anna Bibby
01/08/2020

Nick Maskell
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And finally, to Pippa, sine qua non.

ABBREVIATIONS

AE	Adverse event
ANOVA	Analysis of variance
APC	Antigen presenting cells
BCG	Bacillus Calmette–Guérin
BCG-cws	Bacillus Calmette–Guérin cell wall skeleton
BLF	British Lung Foundation
CACE	Compliance-adjusted causal effects
CFU	Colony-forming units
CI	Confidence interval
CmRCT	Cohort multiple RCT
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete response
CRF	Case report form
CRN	Clinical Research NEtwork
CRP	C reactive protein
CRS	Cytokine release syndrome
CT	Computed tomography
CTA	Clinical trials authorisation
CTIMP	Clinical trial of an investigational medicinal product
CTL	Cytotoxic T lymphocytes
CTLA-4	Cytotoxic T lymphocyte associated protein 4
CXR	Chest radiograph
DCE	Discrete choice experiment
DCR	Disease control rate
DMC	Data monitoring committee

ECMO	Extra-corporeal membrane oxygenation
EMA	European Medicines Authority
EU	European Union
FBC	Full blood count
FDA	United States Food and Drink Administration
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GMP	Good Manufacturing Practice
GP	General practitioner
HES	Hospital Episode Statistics
HR	Hazard ratio
HRA	Health Research Authority
IASLC	International Association for the Study of Lung Cancer
ICD-10	Tenth International Classification of Disease
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICI	Immune checkpoint inhibitors
IFN-α	Interferon alpha
IFN-γ	Interferon gamma
IL-6	Interleukin-6
IL-10	Interleukin-10
IL-12	Interleukin-12
IMD	Index of multiple deprivation
IMP	Investigational medicinal product
IP-10	IFN-γ-induced protein-10
IPC	Indwelling pleural catheter
IQR	Interquartile range

ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention to treat
KE	Klinishe Einheit
LDH	Lactate dehydrogenase
LFT	Liver function tests
MA	Marketing authority
MDT	Multidisciplinary team
MHRA	Medicines and Healthcare Products Regulatory Agency
MPE	Malignant pleural effusion
MPM	Malignant pleural mesothelioma
mRECIST	Modified response evaluation criteria in solid tumours
MRI	Magnetic resonance imaging
NEL	Non-expandable lung
NHS	National Health Service
NICE	National Institute of Health & Care Excellence
NIHR	National Institute of Health Research
NK	Natural killer
NSCLC	Non-small cell lung cancer
ONS	Office of National Statistics
OPCS-4	Office of Population Censuses and Surveys Classification of Interventions and Procedures
OR	Odds ratio
OS	Overall survival
PCT	Primary Care Trust
PD	Progressive disease
PD-1	Programmed death 1 receptor
PDGF	Platelet-derived growth factor
PD-L1	Programmed death 1 receptor ligand

PFS	Progression-free survival
PIC	Participant identification centre
PIS	Participant information sheet
PP	Per protocol
PPI	Patient and public involvement
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta Analyses
PROMs	Patient-reported outcome measures
PS	Performance status
QoL	Quality of life
QP	Qualified person
RCT	Randomised controlled trial
ROBINS-I	Risk Of Bias In Non-randomised Studies of Interventions
SAE	Serious adverse event
SD	Stable disease
SIGLE	System for Information on Grey Literature in Europe
SSAg	*Staphylococcus* superantigen
TGF-β	Transforming growth factor beta
TILT	Trial of Intra-pleural Bacterial Immunotherapy
TNF-α	Tumour necrosis factor alpha
TNM	Tumour node metastasis
Treg	Regulatory T cell
TUS	Thoracic ultrasound scan
TwiC	Trial within a cohort
U&E	Urea and electrolytes
USM	Urgent safety measure

VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor
WS	Work Stream

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Chapter 1 - Introduction

1.1. Background

Mesothelioma is an aggressive cancer caused by previous exposure to asbestos.(1) It affects the outer lining of the lung (malignant pleural mesothelioma, MPM) most frequently, but can also be found in the abdomen (peritoneal mesothelioma), the lining of the heart (pericardial mesothelioma) and rarely the genitals (tunica vaginalis mesothelioma).(1-3) Mesothelioma is incurable, with limited treatment options and a median survival of less than 12 months from diagnosis.(1-3) The current standard of care consists of combination platinum-based chemotherapy alongside pemetrexed, which extends median survival by approximately 2-3 months compared with single agent platinum regimens.(4, 5) Adding bevacizumab to chemotherapy provides a further 3 month survival benefit, but this agent is not currently recommended by the National Institute of Health and Clinical Excellence (NICE) for use in MPM in the UK.(6)

Immunotherapy is a form of treatment which uses the individual's immune system to attack cancer cells. It has revolutionised the treatment of several refractory malignancies, including malignant melanoma and non-small cell lung cancer (NSCLC).(7-10) There is a sound immunological rationale for the use of immunotherapy in MPM,(11-13) and early phase trials have shown promising results.(14-17) Full-scale, phase III, randomised trials are underway.

Before the current era of engineered immunotherapeutic agents, bacterial agents were used to stimulate the immune response. Although rudimentary, as bacterial agents tend to stimulate a widespread and non-specific immune response compared to modern

targeted agents, bacterial immunotherapy has the benefit of being able to be administered locally, potentially reducing the risk of side effects.(18) In MPM, bacterial immunotherapy agents can be delivered directly into the pleural cavity via an indwelling pleural catheter – a semi-permanent silicone tube inserted into the chest to drain fluid and ameliorate symptoms in patients with MPM. In the context of drug administration, the pleural cavity tends to act as a "closed box", with minimal absorption of the therapeutic agent into the systemic circulation.(18, 19) This could potentially maximise drug effectiveness by concentrating the therapeutic agent in the immediate tumour environment, whilst limiting side effects elsewhere in the body.

The overall aim of the work described in this thesis was to explore the role of intra-pleural bacterial immunotherapy in MPM, to determine whether a full-scale trial was warranted, feasible and acceptable to patients. The research used a mixed methods approach, culminating in a feasibility trial using an innovative, pragmatic methodology.

1.1.1. Thesis structure

The research aim was addressed via four separate work-streams. Workstream 1 is described in Chapter 2 and comprised a systematic review of the existing data relating to survival outcomes for intra-pleural bacterial agent usage in pleural malignancy. Chapter 3 contains the methods, results and discussion of Workstream 2, a population-based cohort study that used data from Hospital Episode Statistics (HES) to evaluate whether bacteria in the pleural space as a result of pleural infection were associated with survival in mesothelioma. Workstream 3 consisted of a feasibility trial of two intra-pleural bacterial immunotherapy agents in MPM and is reported in Chapter 4. The trial,

called TILT, was based on the trial within a cohorts (TwiC) design, with the primary objective of determining whether the methodology was practical and achievable in this patient population. The acceptability of the trial to participants and their family members was explored in qualitative interviews, undertaken in Workstream 4 and summarised in Chapter 5. Workstream 4 also explored the experience of living with MPM and of receiving the trial agents. Chapter 6 contains a discussion of the findings of all four Workstreams, interpreted in relation to the existing literature and each other, with a view to informing future research trials.

The remainder of this chapter will provide an overview of mesothelioma (section 1.2), including pathogenesis, clinical presentation and prognosis. This will be followed by a description of immunotherapy in MPM (section 1.3), culminating in a description of the two bacterial agents used in the subsequent trial, OK432 and Bacillus Calmette–Guérin (BCG). The chapter will then describe the TwiC methodology and its benefits and limitations (section 1.4), before closing with an outline of the overall research plan and its stated aims and objectives (section 1.5).

1.2. Mesothelioma

1.2.1. Overview

Malignant pleural mesothelioma (MPM) is an aggressive cancer of the outer lining of the lung (Figure 1.1). Mesothelioma can also affect the peritoneum, pericardium and tunica vaginalis, although these forms of disease are less common.(1) There are three main histological sub-types: epithelioid, sarcomatoid and biphasic or mixed, with prognosis varying depending on type.

1.2.2. Pathogenesis

The majority of mesothelioma cases are caused by previous exposure to asbestos. Asbestos, a naturally occurring silicate mineral, was once considered an ideal construction material due to its high tensile strength, ability to withstand high temperatures and low cost.(20) Indeed its very name is a derivation from an ancient Greek word, ἄσβεστος, meaning "inextinguishable". It was widely used in several industries throughout the 1960s, 70s and 80s. Asbestos has two different structural forms - curly, serpentine fibres of chrysotile, or 'white' asbestos and sharp, needle-like fibres of amphibole asbestos. The latter is further divided into crocidolite (blue), amosite (brown), and anthophyllite, actinolite and tremolite asbestos. Heavy or prolonged exposure to any type of asbestos fibre increases the likelihood of developing MPM, however, the risk is highest following exposure to amphibole fibres.(1, 21)

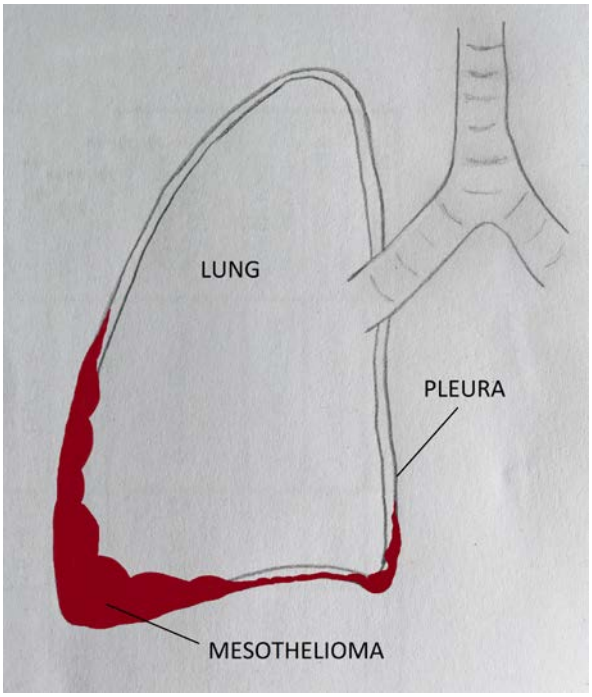


Figure 1.1 Malignant pleural mesothelioma

The mechanism of carcinogenesis in mesothelioma is multifactorial. Asbestos fibres are inhaled and migrate to the pleura. Within the pleural space, fibres cause irritation and a repeated cycle of tissue damage and repair is established. The presence of oxygen free radicals, released by asbestos fibres when phagocytosed by macrophages, causes intra-cellular DNA damage and abnormal repair.(22) Asbestos fibres also penetrate mesothelial cells, where they interfere with mitosis, cause mutations in DNA and alter chromosome structure. Asbestos-exposed mesothelial cells release inflammatory cytokines, including transforming growth factor β (TGF β), platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF).(22) This creates a favourable micro-environment for tumour growth. Finally asbestos induces the phosphorylation of various protein kinases, leading to increased expression of proto-oncogenes and further promotion of abnormal cellular proliferation.(23)

1.2.3. Epidemiology

The ancient Roman scholar and natural scientist, Pliny the Younger was the first to notice the potential harmful effects of asbestos. He observed that people who worked in asbestos mines would often suffer from a mysterious respiratory illness that he called the “disease of slaves”.(24) To protect against this, he advocated the use of a goat or lamb bladder as a rudimentary respiratory filter, although history does not relate whether this was an effective intervention.

The link between asbestos and cancer was first reported in 1935, but it took another 20 years before MPM was described and a direct causal link was determined.(25-27) Attempts to reduce exposure to asbestos dust date back to the Asbestos Industry

Regulations document of 1931, but guidelines were poorly followed and several companies continued to wilfully expose their workers to asbestos whilst fully aware of the risk to their health.(20) In October 1965, this shameful practice was exposed via a front-page article in the Sunday Times, entitled "Scientists track down killer dust disease", which clearly articulated the link between exposure to asbestos and the development of MPM. In the article, it was stated that companies had known about the dangers of asbestos for years and should have taken steps to protect their workforce. This, combined with a change in legislation relating to the period of limitation, resulted in the first successful legal claim for damages in 1967.(28) A voluntary industry ban on blue (crocidolite) asbestos was introduced the same year in the UK, with a similar voluntary ban on brown (amosite) asbestos following in 1980. However, a formal ban of the import and use of crocidolite and amosite asbestos was not imposed until 1985 and it took a further 14 years before white (chrysotile) asbestos was banned outright in 1999. Sadly, many countries around the world, including the US, Russia and Brazil continue to use, mine and export asbestos, despite its harmful effects.

There is a latency period of 30 to 50 years between exposure to asbestos and presentation with MPM.(1, 22, 29-31) As a result, despite the legislation described above, UK and global incidence of mesothelioma has risen steadily over the past 4 decades and continues to do so. Precise numbers are difficult to determine as the disease is likely to be underreported in areas of low incidence and in low and middle income countries. However, an estimate based on 2008 data suggested an average of 14,200 new cases worldwide each year.(32)

The UK has one of the highest mesothelioma mortality rates in the world, with 2542 people dying from the disease in 2015.(33) Incidence is predicted to peak in the UK this year (Figure 1.2), however the ongoing, unregulated use of asbestos in countries with high population densities, such as India, China and Russia, means that mesothelioma will continue to represent a significant global health concern even after peak incidence has passed.(34-37)

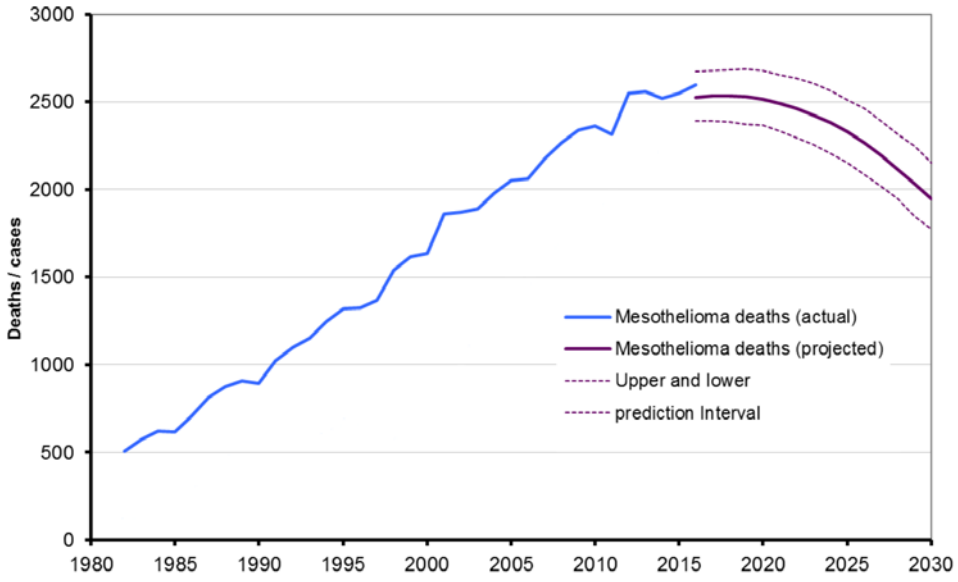


Figure 1.2 Mesothelioma deaths, actual and predicted, in the UK until 2030. Figure reproduced from the UK Health & Safety Executive - Mesothelioma mortality in Great Britain 1968-2015.(33)

The industrial nature of mesothelioma means that there is a male predominance, with a male to female ratio of approximately 4:1.(38) Many women with mesothelioma have a history of para-occupational exposure, for example washing their husband's overalls, although some have been exposed directly from buildings during their schooling or through their own work.

1.2.4. Clinical presentation

Over 85% of people with MPM present with a pleural effusion, where fluid has built up around the outside of the lung.(39) This causes breathlessness in most, and chest pain in many. Symptoms caused by pleural effusions can be managed by chemical pleurodesis (instilling an inflammatory agent into the pleural space to promote adhesion of the two pleural surfaces) or insertion of an IPC (Figure 1.3).(40) If an IPC is inserted, it creates the possibility of delivering therapeutic agents directly into the pleural cavity via the catheter.(41, 42)

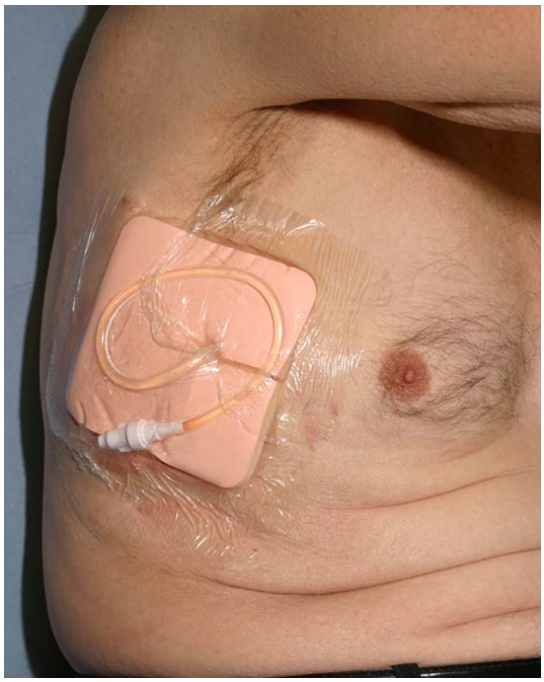


Figure 1.3 An indwelling pleural catheter (IPC)

Breathlessness can also arise as a result of the tumour impeding respiratory dynamics, particularly in late disease when the tumour encases the lung. Extensive tumour or bulky disease can also lead to “trapped” or non-expandable lung (NEL), where the lung

is unable to inflate fully to fill the hemi-thorax, and fluid build-up is inevitable.(39) Chest pain can also occur as a result of direct tumour invasion into the chest wall.

Extra-pulmonary symptoms such as weight loss and fatigue are often present in MPM and occur as a result of tumour cytokines in the systemic circulation and the host's response to the tumour. Fevers and sweats, also due to tumour cytokines and host response, are common in MPM and are particularly difficult to manage.

1.2.5. Prognosis

Prognosis is poor in MPM, with median survival ranging from 8 to 14 months from diagnosis.(29, 30, 38, 43) Of the different histological sub-types, sarcomatoid MPM is associated with the worst outcomes, with median survival just 4 months. In contrast, epithelioid sub-type has the most favourable prognosis with a median survival of 13.1 months.(29, 38, 43) These median values do not tell the whole story, however, as there are some people with remarkably long survival, up to ten years or longer. Female gender, younger age at diagnosis and good functional status are some of the factors associated with longer survival, however there is no reliable biomarker or test that can identify "long survivors" at initial presentation. The most useful prognostic tool is a decision tree developed by Brims et al (Figure 1.4) that uses readily-available clinical factors to separate patients into four groups, with varying estimates of life-expectancy associated with each.(44)

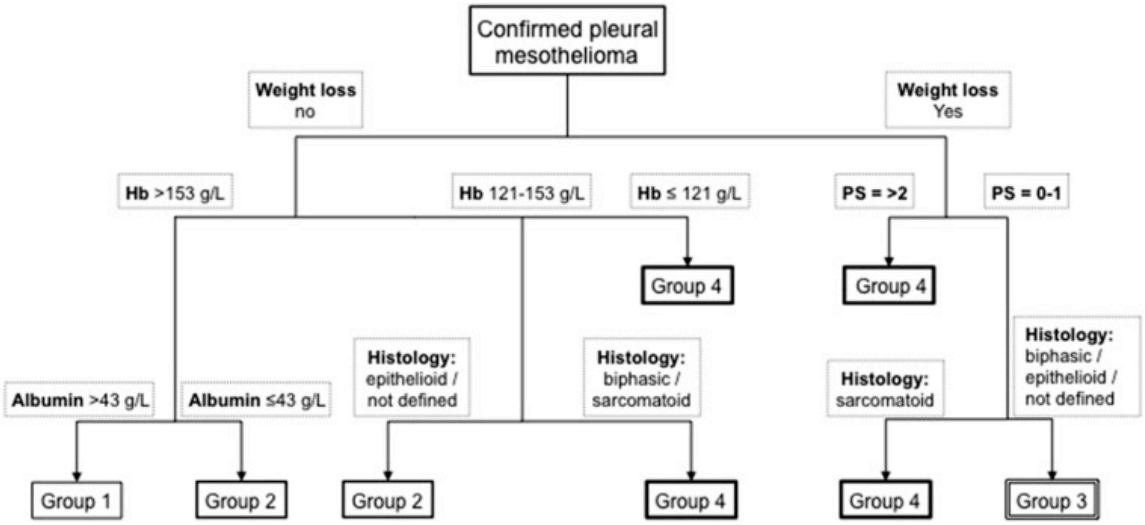


Figure 1.4 Prognostic decision tree for malignant pleural mesothelioma. Figure reproduced from Brims et al - A novel clinical prediction model for prognosis in malignant pleural mesothelioma using decision tree analysis.(44)

1.2.6. Treatment options

Treatment options are limited in MPM, and none are curative. Systemic anti-cancer therapy is the only treatment modality that has been shown to improve survival in randomised controlled trials (RCT).(4, 5) However, prior to 2003 the evidence was poor, with one large RCT demonstrating that chemotherapy offered no survival benefit and no improvement in quality of life (QoL) compared with active symptom control.(45) The lack of available treatment options led to widespread medical nihilism – an attitude that has fortunately changed over the past decade as the increased number of MPM trials has yielded more options and a more hopeful outlook.

1.2.6.1. Chemotherapy

In 2003, two pivotal phase III trials were published that changed the landscape of chemotherapy in MPM.(4, 5) The trials investigated, respectively, two third-generation anti-folate agents, pemetrexed and raltitrexed, which inhibit DNA synthesis and prevent

tumour proliferation. Both trials combined the anti-folate agent with cisplatin and found that the combination regimen was associated with a survival benefit of approximately 3 months compared with cisplatin alone. As a result, Pemetrexed was approved by global marketing authorities for use in MPM in combination with cisplatin.

Over 15 years later, pemetrexed and cisplatin doublet remains the standard first-line chemotherapy regimen. This is despite the fact that overall response rates to chemotherapy were low – approximately 40% in the trials and just 26% when the drugs were rolled out in the US as part of an expanded access programme.(4, 46, 47) Awareness of the marginal benefits alongside concern about potential side effects may explain the variation in chemotherapy uptake around the UK, with less than 50% of eligible people choosing to receive it in some UK centres.(38, 48)

1.2.6.2. Targeted therapy

More recently, the VEGF antagonist, bevacizumab, was shown to prolong survival when used alongside standard chemotherapy in MPM.(6) The multicentre, phase III MAPS trial randomised 448 participants to receive cisplatin and pemetrexed with or without bevacizumab. Patients who received bevacizumab had a median survival of 18.8 months (95% confidence interval (CI) 15.9-22.6) compared with 16.1 months (14.0-17.9) in the chemotherapy alone arm (p=0.017). Bevacizumab treatments was also associated with longer progression-free survival (PFS) and similar adverse event rates, leading the authors to conclude bevacizumab is warranted alongside first-line standard chemotherapy in patients with unresectable MPM. However, in the UK, bevacizumab

has not been recommended by NICE and access is limited. It is available in Europe since gaining marketing authorisation from the European Medicines Agency for use in MPM.

New treatment options are desperately needed for MPM and immunotherapy has shown promise in early phase trials.(15, 49-54)

1.3. Immunotherapy

1.3.1. Background

In 2013, immunotherapy was declared the scientific breakthrough of the year by *Science* Journal.(55) However, the concept of harnessing the immune system to target tumours was not a new one, indeed as far back as 1890, Dr William Coley was injecting osteosarcomas with *Erysipelas* (a bacterium that causes skin infections, now known as *Streptococcus pyogenes*) in the earliest recorded attempt at cancer immunotherapy.(56) Working in the pre-antibiotic age, his success rates were compromised, predictably, by sepsis-related adverse events. However, the theory behind his work endured, with interest in immunotherapy re-emerging periodically throughout the following century.(57, 58)

The modern era of cancer immunotherapy is dominated by a group of drugs known as immune checkpoint inhibitors (ICI). These agents stimulate T lymphocyte activity by blocking inhibitory receptors ("checkpoints") on the T cell surface, thus preventing the cell from being downregulated (Figure 1.5). Specific checkpoints that have been targeted are the programmed death 1 (PD-1) receptor and its ligand, PD-L1, as well as the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). ICI agents that block PD-1,

PD-L1 or CTLA-4 have been shown to improve survival in malignant melanoma, NSCLC and renal cell carcinoma, and are now included in the standard care pathways for these tumours.(8, 10, 59-66) Fittingly, given the impact these agents have had on several poor-prognosis malignancies, the two scientists who identified the immune checkpoints and enabled the development of ICI, Drs Tasuku Honjo and James P. Allison, were jointly awarded the Nobel Prize in Medicine in 2018.

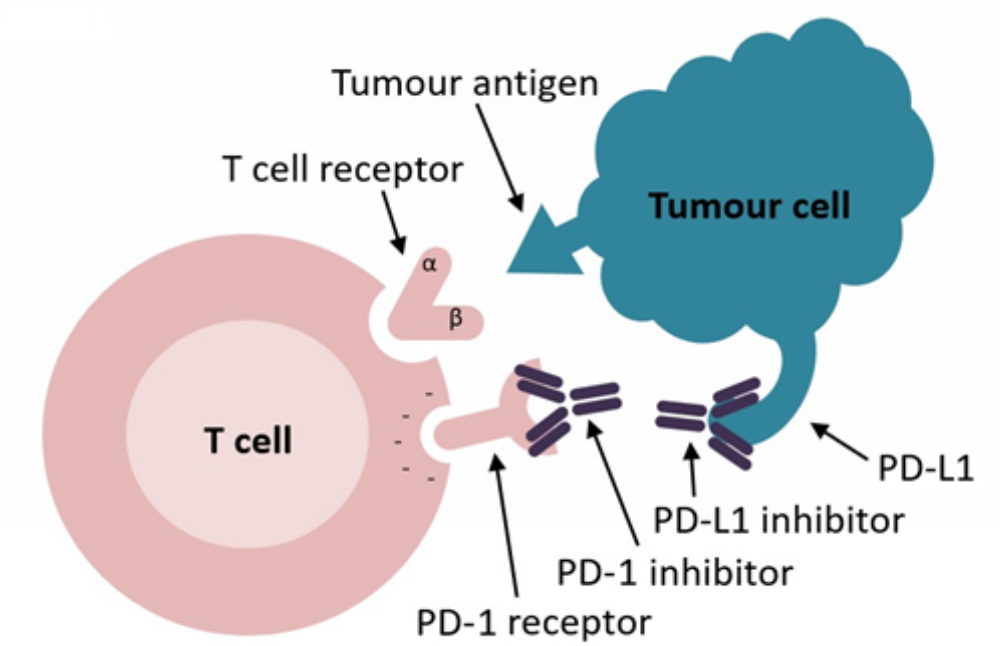


Figure 1.5 The immune checkpoint pathway and targets of checkpoint inhibition

1.3.2. The rationale for immunotherapy in mesothelioma

Immunotherapy is an appealing concept in mesothelioma, as it is a tumour with certain immuno-evasive properties. Mesothelioma's propensity to aggressively invade local structures stems, in part, from its ability to suppress local immune cell populations that usually protect against tumour progression. For example, Cytotoxic T Lymphocytes (CTL) and Natural Killer (NK) cells usually respond to tumour antigens, limit tumour growth and enhance tumour killing, however these cells are depleted in the pleura of

patients with MPM.(11, 12, 67, 68) The ability to overcome this local immunosuppression and maintain functional lymphocyte populations in the tumour environment is associated with longer survival in MPM.(13, 69, 70)

1.3.3. Immune checkpoint inhibition in mesothelioma

Several ICI have been investigated in MPM, the first of which was the CTLA-4 antagonist, tremelimumab. Although phase II data looked promising, a subsequent RCT demonstrated no difference in overall survival (OS) between patients treated with tremelimumab or placebo.(50, 51) A potential explanation for this disappointing result lies in the different functions of the CTLA-4 and PD-1 receptors. CTLA-4 is involved in priming CD4 + memory and helper T cells, whilst PD-1 is predominantly expressed on, and involved in the inhibition of, CD8+ effector T cells.(71, 72) It is possible, therefore, that PD-1 blockade may be more effective than targeting CTLA-4, particularly in PD-L1 expressing tumours such as mesothelioma.

ICI targeting the PD-1 receptor or its ligand PD-L1 have also been investigated in MPM. Like tremelimumab, early phase studies were encouraging. The phase 1b KEYNOTE-028 saw pembrolizumab (a PD-1 inhibitor) given to 25 patients who had previously received chemotherapy. Disease control, defined as a partial response or stable disease following treatment, was seen in 18 (72%) of participants.(14) Another single-arm study of pembrolizumab (NCT02399371) demonstrated similar disease control rates (DCR) of 66% (41/65), with median PFS of 4.5 months (95% CI 2.3 to 6.2) and median OS of 11.5 months (95% CI 7.6 to 14) in previously-treated MPM patients.(73) However, subsequent clinical data from 93 patients treated with pembrolizumab off-label

reported slightly lower DCR of 48%, and median OS of 7.2 months compared with 18 months in KEYNOTE-028.(74) A phase III RCT of pembrolizumab in the second line setting (PROMISE, NCT02991482) reported initial results at the European Society for Medical Oncology Conference in October 2019. The trial failed to meet its primary endpoint of improved PFS compared with second-line chemotherapy. PFS was 2.5 months (95% CI 2.1-4.2) in patients treated with pembrolizumab, compared with 3.4 months (95% CI 2.2-4.3) in those treated with gemcitabine or vinorelbine.(75) Full publication of the results is awaited.

Another PD-1 inhibitor, nivolumab has been investigated in MPM in three phase II trials, NivoMes, MAPS2 and MERIT. In the former, 16 patients out of 34 (47%, 95% CI 30%–65%) demonstrated disease control at 12 weeks after treatment with single agent nivolumab, with an acceptable toxicity profile.(16) Similarly, in the nivolumab arm of MAPS2, 24 of 54 (44%, 95% CI 31–58) patients treated with single-agent nivolumab had disease control at 12 weeks.(17) More recently, the Japanese MERIT study demonstrated DCR of 68% (95% CI, 50.8–80.9) in 34 patients treated with nivolumab in the second- or third-line setting.(76) Reponses persisted with a median duration of response of 11.1 months and median OS 17.3 months. Randomised comparative data is awaited from the phase III CONFIRM trial (NCT03063450), which is expected to report in the final quarter of 2021.(77)

A single PD-L1 antagonist has been trialled in MPM, in a phase 1b, dose expansion cohort study called JAVELIN. Fifty-three, heavily pre-treated patients with pleural and peritoneal MPM were given avelumab, with the aim of evaluating safety and initial

efficacy.(78) Five patients had a complete or partial response, giving an overall response rate of 9% (5/53, 95% CI, 3.1%-20.7%). Responses were long-lasting, with a median duration of response of 15.2 months (95% CI 11.1–not estimable). A further 26 patients (49%) had stable disease, generating a DCR of 58%. Median PFS was 4.1 months (95% CI 1.4 to 6.2) and median OS 10.7 months (95% CI 6.4 to 20.2). The drug had an acceptable toxicity profile with only 5 treatment related adverse events and no treatment related deaths.

The only ICI that has been used in the first-line setting for MPM is durvalumab. In the single-arm, phase II DREAM study, 54 treatment-naïve patients were treated with durvalumab alongside standard pemetrexed and cisplatin chemotherapy.(79) The overall radiological response rate was 48% (26/54, 95% CI 35-61%), with disease control achieved in 87% (47/54). Median PFS was 6.9 months (95% CI 5.5-9.0) with an estimated 1-year survival rate of 65% (95% CI 54-79) after 24.6 months follow-up. However, side effects were common, with 36/54 participants experiencing one or more adverse event of grade 3 or higher.

Given the distinct immunological functions of the PD-1 and CTLA-4 receptors, it is possible that the effect of blocking one in isolation is limited if the other pathway remains uninhibited. Experience in the melanoma field supports this hypothesis, with evidence that the combination of ipilimumab (a CTLA-4 antagonist) and nivolumab produced a synergistic effect on survival outcomes compared with either agent alone.(61-63)

The same combination of agents were trialled in MPM in the CHECKMATE-743 trial. This randomised, open-label, phase III trial compared the survival benefit of nivolumab plus ipilimumab with standard chemotherapy in the front-line setting. The results were presented for the first time at the Virtual Presidential Symposium at the World Conference on Lung Cancer in August 2020. The primary outcome, overall survival, was 18.1 months in the ipilimumab and nivolumab arm, compared with 14.1 months in the standard chemotherapy arm, producing an adjusted hazard ratio for mortality of 0.74 (95% CI 0.6-0.9).(80) Combination therapy appeared to be most effective in patients with greater than 1% tumour PDL1 expression and in people with sarcomatoid disease, although these analyses were unadjusted. There were a similar number of adverse events in the two arms, although the nature of the events differed in accordance with the known side effects of the different regimens. There were more serious adverse events and a higher number of treatment discontinuations in the immunotherapy arm, but these participants had a longer duration of treatment overall, which may explain this finding. The full report of the trial is awaited, and is likely to change practice with regard to the frontline standard of care in MPM.

The combination of ipilimumab and nivolumab has also been investigated in previously treated MPM in phase II trials. In the MAPS2 study, patients randomised to the combination arm were treated with ipilimumab plus nivolumab.(17) Twenty-seven patients of 54 (50%, 95% CI 37–63) exhibited disease control at 12 weeks, with a median OS of 15·9 months (95% CI 10·7–not reached). For a drug regimen given in the second- and third-line setting, where the best recorded median OS for chemotherapy is 10.5 months, this potentially represents a clinically meaningful benefit.(81) Published

simultaneously, the INITIATE trial was a single arm study of nivolumab plus ipilimumab also in the second- or third-line setting. Twelve-week DCR was higher than in MAPS2 at 23 out of 34 patients (68%, 95% CI 50–83) with median survival not attained after 14.3 months of follow up.(15) Phase III trials are planned.

Tremelimumab has also been tested in a combination regimen, alongside durvalumab. Phase II data showed the combination to be safe and potentially effective, but an RCT is required to confirm this observation.(82)

1.3.4. Intra-pleural bacterial immunotherapy

Like chemotherapy, ICI are intra-venous agents, with the potential to cause systemic side effects, including potentially fatal complications.(17) The increased use of IPCs in MPM (and other malignancies) offers an opportunity to deliver drugs directly into the tumour environment, which may limit systemic absorption and lead to fewer side effects.(18, 19) Further laboratory and animal studies are necessary to ascertain whether intra-pleural use of ICIs is safe in humans.

As mentioned previously, the earliest attempts at cancer immunotherapy used bacteria to stimulate the immune response. Bacterial agents - commercial products made up of altered or attenuated bacterial components - have been delivered into the pleural space for decades as pleurodesis agents. In the UK, *Corynebacterium parvum*, a gram positive aerobic bacillus, was used as a pleurodesis agent for malignant pleural effusions (MPE) between 1970 and the late 1990s.(83-87) Some clinicians believed *C. Parvum* exerted an additional, anti-tumour effect, although others disputed this.(88-91) Eventually the

commercial preparation (which was never actually licensed for use in humans) ceased production.

There is a scientific rationale supporting the hypothesis that bacterial agents may have antic-cancer activity. As part of the inflammatory process that results in pleurodesis, bacterial agents stimulate effector immune cells.(92) Some of these cells, specifically CTL and NK cells have concomitant anti-cancer activity. In addition, bacterial agents induce the release of multiple cytokines, including tumour necrosis factor α (TNF-α) and TGF-β, which have tumour suppressive effects.(93)

Based on this theory, research groups in Asia rekindled an interest in intra-pleural bacterial immunotherapy for pleural malignancy. Clinical trials were undertaken using *Staphylococcus* superantigen, *Lactobacillus casei* and killed *Streptococcal* preparations in patients with MPE secondary to lung cancer.(94-96) Results were encouraging, but participant numbers were small. To date, the effect of bacterial agents in MPM has not been studied.

This research focussed on two bacterial agents; OK432 and BCG, administered intra-pleurally via an IPC to patients with MPM.

1.3.5. OK432

OK432 is a heat- and penicillin-killed, freeze-dried preparation of *Streptococcus pyogenes*. Preparation involves heating live streptococci to 37°C in the presence of penicillin. This temperature is maintained for 20 minutes before being raised to 45°C for

30 minutes.(97) This eliminates the proliferative ability of the organism and inactivates its capacity to produce toxins. Thus, while bacterial cell structure remains intact, active streptococcal infection following administration is not possible.

In vitro, OK-432 induced lymphocyte-mediated tumour killing in pleural fluid, whilst *in vivo*, it has been associated with longer survival in several cancer types.(98-100) In non-small cell lung cancer, meta-analysis of trial data demonstrated longer survival in patients treated with OK432, with an odds ratio (OR) of 0.70 (95% CI 0.56 to 0.87) for mortality.(100) However, whilst the studies included in the meta-analysis delivered OK432 intra-tumourally, sub-cutaneously or intra-venously, intra-pleural administration was not included.

Five randomised trials compared intra-pleural OK432 with other intra-pleural or intra-venous chemotherapy agents in people with MPE.(96, 101-104) All five focussed on control of the pleural effusion rather than survival or other cancer-specific outcomes, however, two reported longer survival in patients treated with OK432 and chemotherapy compared with either agent in isolation.(101, 104) Neither study was adequately powered for this outcome though, and both were at high risk of bias in at least one area of their methodology.

Intra-pleural OK432 has been demonstrated to be an excellent pleurodesis agent and has been used in the routine management of MPE in Japan since the 1980s.(96) Adverse events are rare. In phase IV data from 26,027 patients treated with OK432 prior

to 1984, inflammation at the injection site and fever were the most frequent and severe toxicities seen. These occurred in 23% and 15% of patients respectively.

1.3.6. BCG

BCG is a live, attenuated, low-virulence strain of *Mycobacterium bovis*, currently used as a vaccine against tuberculosis. In addition to stimulating CD4+ and CD8+ cytotoxic T lymphocytes and eliciting the production of anti-cancer cytokines, BCG produces a delayed type IV hypersensitivity reaction, mediated by T helper cells, which enables sustained anti-tumour activity alongside the acute inflammatory response.(105-107).

BCG has been shown to have anti-tumour activity in skin and bladder cancer, and has been used as an intra-cavity anti-cancer agent in bladder cancer since 1976.(108) Meta-analysis of RCT data demonstrated that intra-vesical BCG reduced the risk of progression in non-invasive bladder cancer compared with no treatment or other intra-vesical therapies.(109-113) Bladder biopsies taken from patients treated with intra-vesical BCG demonstrated induction of antigen presenting cells and macrophages, with associated T cell-predominant inflammation for up to 6 months after treatment.(114)

In malignant melanoma, BCG injected into the tumour was associated with regression of up to 90% of the targeted lesion, and an abscopal effect of over 15% tumour reduction in non-treated lesions.(115) This occurred in conjunction with significant prolongation of disease-free periods and longer overall survival, even in patients with metastatic disease. In recent years, however, BCG has been superseded by ICI in melanoma treatment.(62, 63, 66)

Finally, observational data from a 60-year follow up study of 2963 patients who participated in an RCT of BCG vaccination as children, suggested a possible protective effect from lung cancer later in life. Lung cancer rates were 18.2 per 100,000 person years in people vaccinated with BCG, compared with 45.4 per 100,000 person years in the group who received placebo (hazard ratio (HR) 0.38, 95% CI 0.20-0.74).(116) The authors hypothesise that generation of CD4+ memory and natural killer cells following BCG vaccination enables later activation of these immune cells with smaller stimulus, and therefore enhanced anti-cancer detection and activity.

Intra-pleural BCG was investigated as an adjuvant therapy to surgery and chemo-radiotherapy in the 1970s. Early studies demonstrated that it was feasible and safe to deliver BCG intra-pleurally.(58, 117, 118) Furthermore, intra-pleural BCG was associated with a reduction in recurrence rates, and an overall survival benefit compared with placebo.(58, 118-123) The evidence was conflicting however, with a similar number of trials demonstrating no difference in survival following intra-pleural BCG.(124-129) A small number of studies suggested intra-pleural BCG was associated with worse outcomes,(117, 130) although in one of these BCG (without chemotherapy) was compared with standard chemotherapy – a design that would be deemed unethical in the current day, as it entailed withholding an established efficacious treatment from a proportion of participants.(130) Additionally several of the negative studies were non-randomised,(125, 126) and many involved small participant numbers and were likely underpowered to detect differences in survival.(117, 127, 128)

Another explanation for the different outcomes observed in BCG trials may lie in the different BCG strains used. It has been established that TICE strain is more effective than Connaught strain, and of the lyophilised vaccines, Pasteur is more effective than Glaxo.(131, 132) It may be relevant, therefore, that three of the six trials that demonstrated a positive effect of BCG used the TICE strain.(58, 119) For this reason, TICE strain was selected for use in this research.

Whether or not intra-pleural BCG was effective in lung cancer, there remains a strong case for potential efficacy in MPM. Mesothelioma is similar to melanoma, both in terms of histological appearance and certain genetic mutations driving the tumours.(133, 134) In addition, as a localised tumour affecting a discreet body cavity, MPM resembles early-stage bladder cancer and offers a similar opportunity for targeted delivery of anticancer drugs directly into the tumour environment. Animal studies have shown that proximity of BCG to tumour was an important factor in producing an effective response.(135) Unlike lung cancer, where intra-pleural administration was anatomically distant from the original site of disease, intra-pleural administration in MPM delivers the drug into direct proximity with the tumour, thus creating immune stimulation in the very area it will be most effective.

1.4. The trial within a cohort (TwiC) design

1.4.1. What are TwiCs?

This research used the trial within a cohort (TwiC) design to investigate intra-pleural bacterial immunotherapy in MPM.(136) This is a highly pragmatic methodology that aims to replicate real-life clinical practice, with several potential benefits.

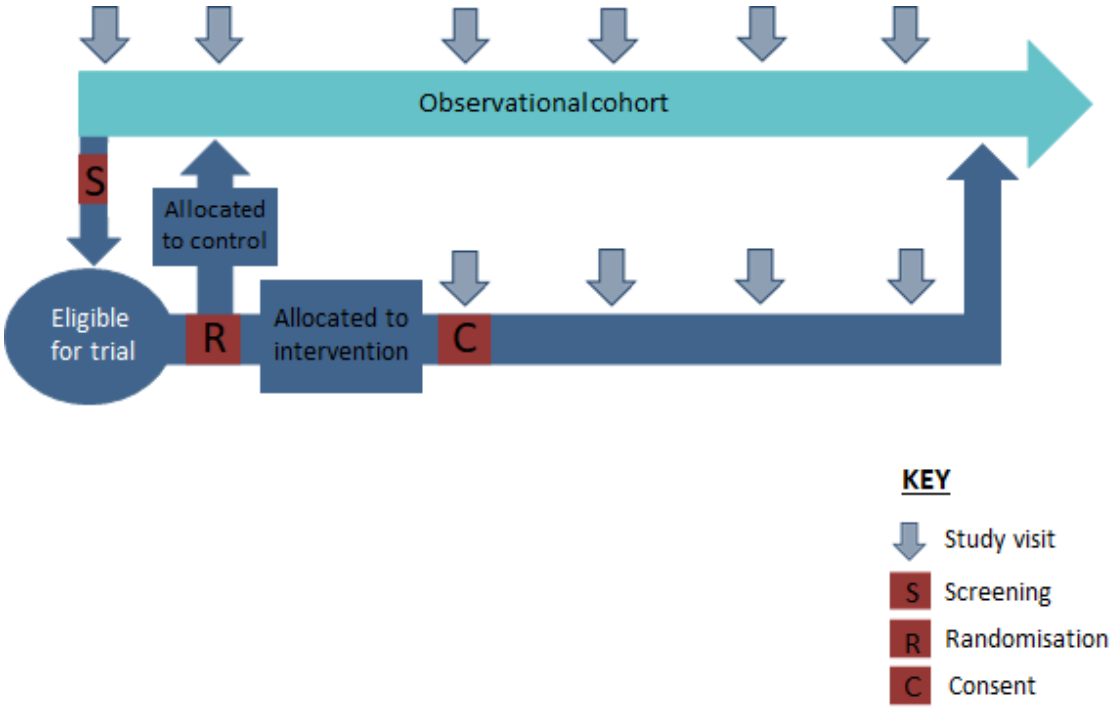


Figure 1.6 Schematic representation of the TwiC methodology

The TwiC design, also known as the cohort multiple randomised controlled trial (cmRCT) methodology, uses data from an established, longitudinal, observational cohort study to screen cohort participants for their eligibility to participate in the trial. Eligible cohort participants are randomly selected to be offered the trial intervention, at which point they are provided with further information about the trial and, with their consent, enrolled. Cohort participants who are eligible for the trial but not randomly selected remain in the cohort and are not informed about the trial or the intervention. Their data is used as control data for the trial. Figure 1.5 shows a schematic representation of the TwiC design.

1.4.2. Ethical considerations of TwiCs

One of the most frequently stated concerns about the TwiC design relates to whether it is ethical. Experienced clinical trial methodologists recognise its similarities to the

historic Zelen design – a trial methodology in which participants were randomised before they provided consent.(137) Since randomisation is inarguably a research activity, this constituted a breach of patient autonomy based on both the Declaration of Helsinki, which states that "subjects must be volunteers and informed participants in the research project", and the United Nations International Covenant on Civil and Political Rights statement that "no one shall be subjected without his free consent to medical or scientific experimentation."(138)

There are, however, certain situations where it may be necessary to conduct a trial without consent, e.g. in emergency settings, where the process of obtaining consent would delay treatment and therefore not be in the patient's best interests, or where it may not be possible to obtain consent due to the patient's clinical condition e.g. unconsciousness. Scott Kim, a prominent American bioethicist, described five conditions where conducting a trial without consent could be potentially ethically justified.(139) These conditions were:

1. Scientific necessity, where the process of obtaining consent undermines the scientific validity of the results or make the trial impossible to conduct. Examples of this include where there is high potential for contamination between arms or a high risk of the Hawthorne effect (where participants' behaviour changes once they are aware they are in a trial).
2. Low risk, where participating in the trial exposes participants to no or minimal risk of harm compared to standard treatment. Such trials usually amount to comparisons of different usual care regimens.

3. Analogous clinical situations, where the intervention would not usually be consented for in clinical practice. There are several settings where this may be the case, including
    a. clinical constraints, e.g. emergency settings as described above,
    b. therapeutic non-disclosure, e.g. where the process of obtaining consent would create psychological harm,
    c. package deal, where the trial intervention is inherently related to other processes and would not usually be consented for e.g. ventilator settings in intensive care, and
    d. cluster trials, where interventions are implemented at a higher level e.g. treatment pathways in general practitioner (GP) services, or impact on aspects of care in which patients do not usually have involvement e.g. medical staffing.
4. Meaningful preference, where there is no clear patient preference for an intervention, or the outcomes under study are not of value to participants.

However, many of these conditions are subjective, for example the assessment of "low risk" for criteria 2, or evaluation of potential psychological harm in criteria 3b. Ultimately, Kim rejected most of the above criteria, believing that only scientific necessity, clinical constraints and certain cluster trials were ethically justifiable to conduct without consent. He concluded that the sole reason to conduct a trial without consent was if the "research cannot practicably be carried out" with consent, the corollary being that if consent can be obtained, it should be.(139)

The Zelen design has been used in some circumstances that meet the criteria described by Kim, e.g. a randomised trial of extra-corporeal membrane oxygenation (ECMO) in neonates who had an 85% likelihood of dying without treatment.(140) In that trial, it was thought to be too distressing to raise parents' hopes by discussing a potential treatment with them during the consent process and then denying them the treatment if their child was randomised to usual care. In that situation, the Zelen design appeared to be a reasonable and justifiable methodology.(141) However, in other situations, by failing to obtain consent from people who were (usually) able to provide it, the Zelen design breached Kim's principle.(138, 142) It was, therefore, concluded to be an unethical approach and one that was potentially harmful to the researcher/participant relationship, and often the doctor/patient relationship too.(137, 138, 143) .

Similar to Zelen, it could be said that randomisation without consent is inherent to the TwiC methodology. With an awareness of the potential ethical pitfalls of the design, its creators organised an international symposium on the ethics of TwiCs in 2016, attended by clinical triallists, bioethicists, research regulators and myself.(144) It was noted that the majority of RCTs failed to recruit to time and target, and there was an ethical consideration to be made relating to inefficiency, wasted resource and squandered participant effort if trials were abandoned or failed to recruit adequate numbers to power the primary outcome. By adopting a radically different approach to participant identification and enrolment, TwiCs could overcome these issues.

Discussion at the symposium included anecdotal concerns that patients in the control arm could be seen as being “deceived” because they were not informed about the trial and “exploited” as their data was used without their knowledge. (142, 144, 145) An elegant solution to this issue was suggested by Dr Danny Young-Afat from Utrecht Medical Centre. He proposed a two-stage consent model in which, on enrolling in the cohort, patients were asked to consent to be screened for future trials, to be randomly selected for the trial and to allow their data to be used as comparison data if they were not selected, without being further informed of this at the time.(146) Trial participants were then approached to give further consent if and when they were randomly selected to join the trial. With this approach, the second consent process was highly specific, as the participant was essentially asked whether they wish to receive the trial intervention or not. This pleasingly addressed another ethical issue that is often overlooked in clinical trials, that of overburdening participants with information, discussed in more detail in the next section.(144)

The two-stage consent process removed the issue of randomisation without consent and of potential deception or exploitation of control patients.(144) It allowed every participant, whether in the cohort or the trial, to give their consent for the exact research processes they would undergo, thus maintaining, indeed enhancing, their autonomy. As discussed in the next section, this approach supported the highly pragmatic nature of TwiCs by replicating real-life clinical care as closely as possible. Following discussion with the trial team and patient involvement groups during the design period, the two-stage consent model was chosen as the most ethically and individually acceptable approach for TILT. In addition, as discussed in section 4.2.1., it

became clear that the two-stage consent model was a pre-requisite if the trial was to be compliant with European Union Clinical Trials Regulations.

1.4.3. Benefits of the TwiC design

The TwiC methodology offered certain benefits over the traditional RCT design.(136) The presence of a cohort allows simultaneous collection of observational data that provides information on the natural history of the disease. Additionally, because cohort studies tend to have broader eligibility criteria than clinical trials, they can recruit more quickly and often enrol participants with more diverse characteristics.(136, 147) This is a significant potential benefit in MPM research, where recruitment can be slow and participant diversity narrow.(50, 148)

The TwiC methodology is highly pragmatic in nature and aims to replicate real life clinical care to a greater degree than occurs with a standard RCT. As a result, TwiCs tend to have high external validity, and are an excellent method of evaluating effectiveness, rather than efficacy.(149) This is particularly pertinent in MPM, where trial populations are often not representative of real-world patients. Indeed, in one observational study of consecutive MPM patients from a single Australian hospital, 55 of 109 patients evaluated (50.5%) did not meet the eligibility criteria for the MAPS study and 42/105 (40%) were ineligible for KEYNOTE-028.(150) This selection bias causes disparity between the efficacy of a drug as reported in clinical trials and the effectiveness of the same agent when rolled out into real-world clinical care. For example, response rates in the original pemetrexed and cisplatin trial were approximately 40%, but only 26% when the drug began to be used in clinical care.(4, 47)

The similarity of TwiCs to real-life clinical practice is most obvious in relation to sharing information with participants. In an RCT, participants are given information about the trial interventions and then randomly allocated to one, meaning that a proportion of people (those allocated to the control arm) have been informed about a treatment or intervention that they do not ultimately receive. In contrast, in clinical practice, patients are provided with information about a specific treatment when it is indicated for their clinical care and, if they agree to it, they will definitely receive said treatment. The patient may choose to decline treatment, based on individual preference or following an evaluation of risks and benefit, but the option to receive treatment is not withdrawn from them. Conversely, patients are not told about treatment that they are not going to receive. TwiCs replicate this by providing information about the intervention solely to participants who have been selected to receive it. As well as making TwiCs pragmatic, this creates a patient-centred or "personalised" consent process, whereby each participant provides consent for the exact research process or intervention that they will undergo, and none that they will not.(136)

The personalised consent process has several specific benefits. Firstly, it can reduce disappointment. In conditions like MPM where treatment options are limited, people may choose to participate in clinical trials in the hope of gaining access to a treatment that is not otherwise available. However, if the trial includes a standard care arm (and is unblinded), participants who were hoping to receive a novel treatment may be disappointed if they are allocated to this arm. They may withdraw from the trial, or the disappointment may be so great it impacts on their quality of life or affects other

patient-reported outcomes. By blinding controls to the existence of the trial and the intervention, the TwiC design removes this issue, and may therefore reduce attrition bias and reporting bias.(136)

The second benefit of person-centred consent is that it can reduce anxiety associated with uncertainty. When invited to participate in an RCT, people are asked to make a decision without knowing what the consequence of that decision is, i.e. they may or may not receive the trial intervention depending on subsequent randomisation. This uncertainty renders the decision-making process harder and more stressful.(151) In contrast, the TwiC design provides patients with a more straightforward choice. Patients are only offered the intervention once they have been selected to receive it, so their decision is simplified to whether they want to receive the intervention or not. The outcome of the decision is known at the point that the decision is made. This relieves the burden of decision-making and reduces anxiety and confusion.(145) It also releases control participants from making additional decisions and avoids them being burdened with unnecessary information.

This is of particular importance in MPM research, as patients are often approached to participate in research studies soon after receiving their diagnosis. They are likely to be dealing with a number of uncertainties, such as “what does the future hold?”, and “how long will I live?”. Adding further uncertainty at this time could be considered unethical or at the very least, unkind.(145)

The TwiC methodology respects patients' choices to decline an intervention and allows data to be collected on non-participants. In an RCT, if an eligible person chooses not to participate when approached about the trial, no data can be collected on them. In contrast, because TwiC participants are already enrolled in a longitudinal cohort, even if they choose not to join a trial, they will have already contributed data to the cohort and, presumably, will continue to do so. This provides useful information about the characteristics of people who choose not to participate in trials and whether their outcomes differ in any way to the trial participants. The data can also be used to assess the representativeness of the trial population with respect to the cohort and, consequently, the generalisability of results.

Once participants have completed the trial, they return to the cohort for ongoing longitudinal follow-up. This enables collection of long-term outcomes relating to the trial intervention, e.g. survival or delayed adverse reactions, without the need for an extended trial period.

Using the TwiC design, multiple trials can be embedded within the same cohort, meaning that participants have repeated opportunities to participate in trials.(136) This is most useful in diseases where different interventions or treatments are needed at different stages in the disease pathway. Caution is required, however, if multiple trials with the same primary outcome are running in the cohort, as contamination is likely to occur between the trials.(152)

1.4.4. Limitations of the TwiC design

All trial methodologies have strengths and weaknesses and the TwiC design is no different. It is important to appreciate the limitations of the methodology and to evaluate whether this approach is suitable and appropriate for the research question being asked. Specifically, there are several considerations relating to the control arm of TwiCs that make them unsuitable for certain types of research.

Firstly, because the TwiC methodology is fundamentally pragmatic, the use of a non-placebo-controlled arm means the design is not suitable for early phase trials aiming to determine whether an intervention works, and how.(136) These questions are best answered by blinded, placebo-controlled efficacy trials.

Secondly, the control arm in a TwiC is, by definition, standard care. It is not suitable, therefore, for conditions where a standard of care has not been established, or where there is wide variability in the usual management of a condition. In this situation, the heterogeneity of treatment in the control arm could make statistical analysis impossible or render the results meaningless.

Whilst embedding a trial within a cohort affords several benefits related to collection of additional cohort data, it is recognised that cohort studies can be time consuming and expensive to set up.(147) Maintaining the cohort can also be demanding in terms of resources, but is of the utmost importance to ensure optimal data quality and low rates of loss to follow-up.(153) Additionally, for the control arm to provide valid comparison data, follow-up visits for controls in the cohort must match those of the trial, both in

terms of content and timing. For this to be manageable, a degree of flexibility is required within the cohort. This is only achievable if the cohort protocol is designed pragmatically, without an overly proscriptive follow-up schedule.

Similarly, for cohort participants to be effectively screened for their eligibility to participate in a TwiC, the cohort must collect data relating to the trial inclusion and exclusion criteria. A recent TwiC of an exercise intervention in patients with breast cancer highlighted this issue when 48% (62/130) of patients randomly selected to receive the intervention were subsequently found to be unsuitable on further investigation.(154) To prevent the study being underpowered, the sample size had to be increased, although fortunately one of the benefits of the TwiC design came into play, and recruitment was completed swiftly, with the existing cohort providing a resource for potentially suitable participants.

There is an important statistical point to be aware of with TwiCs. Because control participants are blinded to the existence of the trial and are not asked to give further consent after randomisation, they do not have the opportunity to decline participation. This is ethically acceptable, since they have consented to provide control data for trials when they enrolled in the cohort, however it may lead to problems with differential attrition. As long as controls continue to participate in the cohort and are not lost to follow-up, they will provide complete data, with no attrition in the control arm. In contrast, patients selected for the intervention are given the participant information sheet (PIS) and given time to consider whether they would like to receive the intervention, before being asked to provide consent for the trial. There is potential for

some patients to choose not to enrol at this point. Equally, if the trial intervention consists of multiple processes, e.g. repeat doses of a drug, a participant may decide not to complete the full course, either due to side effects or a change of heart. Differential attrition could bias the observed effect of intervention in the final results.(155, 156) Arguably, however, the result will be a realistic reflection of the effectiveness of the drug in the real-world setting, which will inevitably include patients who decline to take it or who do not complete the prescribed course. This reflects the pragmatic nature of the TwiC design.

If the potential bias introduced by differential attrition is of concern, various statistical approaches can be employed to adjust for compliance. One such approach is compliance-adjusted causal effects (CACE) modelling, which is a form of instrumental variable analysis.(157, 158) By assuming that a similar proportion of control participants would have been non-compliant given the opportunity, and that the characteristics of the non-compliant populations would be the same in the control and intervention arms, CACE analysis adjusts the effect size in the control arm for conceptual non-compliers.(158) This, as well as other forms of instrumental variable analysis, may reduce the risk of attrition bias in TwiCs.(156) Importantly, CACE analysis produces a result that applies only to compliers, i.e. it yields efficacy data rather than information on effectiveness, and arguable detracts from the pragmatic focus of the TwiC design.

Another consideration for TwiC trials is the potential for contamination if multiple trials are run within the same cohort, especially if the trials are evaluating the same primary outcome.(152) One way of avoiding this is to allow cohort participants to only

participant in one trial, although this removes one of the benefits of the TwiC methodology, namely the opportunity for patients to participate in multiple trials. Additionally, unless there is a rapid turnover within the cohort, preventing patients from participating in more than one trial may lead to selection bias and reduced external validity as fewer and fewer people are eligible to be randomised for sequential trials. An alternative solution would be to ensure that each trial running within the cohort focusses on a different element or stage of the disease pathway with different primary outcomes. For example, in MPM, a trial examining fluid management techniques could co-exist with a trial of an oncological treatment or a trial of palliative care interventions, as the outcome of one trial is unlikely to be affected by the intervention of the other.

At the time of designing TILT, the TwiC design had never been used in the MPM population, nor had it been applied to a clinical trial of an investigational medicinal product (CTIMP). Many of the potential benefits seemed relevant to this patient group, and the potential to facilitate recruitment was attractive. However, there was uncertainty about whether it would be possible to deliver a TwiC in the MPM setting, and whether the design would be acceptable to patients. Consequently, TILT was designed as a feasibility study, aiming to explore these factors and to determine whether a full-scale TwiC of intra-pleural bacterial immunotherapy would be possible in people with MPM.

1.5. Overall study design

This research was developed to test the hypothesis that intra-pleural bacterial immunotherapy may be an effective treatment for MPM, with better tolerability and

fewer side effects that systemically delivered therapies. The hypothesis was investigated from several angles, including a systematic review of the literature relating to intra-pleural bacterial agents in pleural malignancy. This was followed by a cohort study that used population-level data to test the validity of previous "natural experiments", that reported pleural infection was associated with longer survival in pleural malignancy.(159-161) Ultimately an RCT is required to determine whether intra-pleural bacterial agents prolong survival in MPM, and for the reasons described in section 1.4.3., the TwiC design appeared attractive. However, with no such trials having been undertaken in MPM patients before, a feasibility study was necessary to establish whether certain facets of the design would be possible in this population, and whether it was acceptable to participants. Additionally, since the bacterial agents of interest – OK432 and BCG – had not previously been administered to patients with MPM, a feasibility study would provide initial information on tolerability and acceptability and help inform whether a full-scale RCT would be achievable.

1.5.1. Aims

The overall aim of the work described in this thesis was to explore the role of intra-pleural bacterial immunotherapy in MPM, in order to determine whether a full-scale trial of intra-pleural BCG or OK432 in MPM was warranted, feasible and acceptable. The research was designed in response to a James Lind Alliance Priority Setting Partnership for mesothelioma, undertaken in 2015.(162) During that process, a group of clinicians, patients, charities and other stake-holders ranked the top 50 research priorities for mesothelioma in order of importance. The 8th most important research question was whether there is "a role for intrapleural immunostimulants (a drug designed to

stimulate an anti-cancer immune response, such as corynebacterium parvum extract)". The intention was for the findings from this research to contribute to the design of a future randomised trial aiming to answer this question definitively.

To achieve the research aim, four specific sub-questions relating to intra-pleural bacterial immunotherapy were asked. Corresponding workstreams were developed, to address each sub-question, with the intention that, viewed collectively, the results would answer the overall research question.

1.5.2. Objectives

This research had four objectives, based on the four research sub-questions.

- To determine whether the existing evidence supported the hypothesis that intra-pleural bacterial agents are associated with longer survival in patients with pleural malignancy.
- To examine whether bacteria that arose spontaneously in the pleural space, i.e. pleural infection, were associated with altered survival in MPM.
- To explore the feasibility of a randomised trial of two intra-pleural bacterial agents – OK432 and BCG – in MPM, using the TwiC methodology.
- To evaluate the acceptability of the TwiC design and of receiving intra-pleural OK432 and BCG to trial participants and their families.

The objectives were addressed sequentially, by four workstreams:

Workstream 1 was a systematic review that summarised the existing literature relating to intra-pleural bacterial agents in pleural malignancy. It focussed on oncological outcomes, specifically survival and tumour response rates. Information on adverse events was also collated, to inform design of the subsequent feasibility trial.

Workstream 2 was a population-based cohort study that used historic data from Hospital Episode Statistics for all patients with mesothelioma seen in English hospitals over a 10-year period. Linked mortality data was obtained from the Office of National Statistics (ONS). This workstream was designed to determine whether bacteria that arise spontaneously in the pleural space as a result of pleural infection were associated with altered survival in patients with mesothelioma, as had been reported in previous observational studies.(159-161)

Workstream 3 was a prospective, multi-centre, randomised, three arm trial of intra-pleural OK432 *vs* intra-pleural BCG *vs* usual care in MPM. The trial, called TILT, was a feasibility study based on the TwiC methodology, aiming to determine whether the TwiC design could be utilised in this setting, whether intra-pleural OK432 and BCG could be delivered practically and safely, and whether a full-scale trial would be possible.

Workstream 4 was a qualitative study comprised of semi-structured, face-to-face interviews with trial participants and separate face to face interviews with their family members or carers. The study was designed to provide an understanding of the experience of participating in TILT, as well as to explore the knowledge, beliefs and decision-making processes relating to treatment decisions and research participation.

The aim was to determine whether TILT was acceptable to patients and their family members, and to use the insight afforded by the interviews to refine the design of subsequent trials.

1.5.3. Mixed methods research

To tackle the overarching research question, this thesis employed both quantitative and qualitative methods, combining the results to generate more informative findings. This type of research, which is often referred to as "mixed methods", merges diverse methodological approaches from different scientific backgrounds, based on contrasting research paradigms.

Quantitative research was developed from an ontological standpoint, i.e. "the study of being".(163) It assumes an objective reality that exists independent to the researcher and the researcher is simply revealing that reality or investigating how it works, i.e. "what can be known about X?" An extension of ontology is epistemology, which can be defined as the theory of knowledge, exploring how knowledge is formed and how it relates to reality, i.e. "how do we know this about X?"(163) Quantitative research adopts a "positivist" approach, drawing on the ontological and epistemological premise of an objective and independent reality, to test a hypothesis using empirical data. The hypothesis is generated based on existing information, and assessed using observed "facts", collected by an impartial researcher. The findings obtained are intended to describe the observed reality and are therefore considered generalisable.

In contrast, qualitative research methods, which arose from the social science disciplines, assume a more subjective state. They generally argue that reality is not fixed, but rather is individually constructed.(164) Each object or event has a different meaning depending on a person's experience or interpretation of it, which often relate to a social or cultural context. This is referred to, in different contexts, as a "relativism", "interpretivism" or "constructivism". The aim of qualitative research is to develop an understanding of this subjective reality by attempting to understand an individual's experience. Typically, this requires an inductive approach, in which observations are collated to formulate a hypothesis or theory.

Additionally, with qualitative methods, the researcher brings their own individual experience to the research, which informs the way in which they collect and interpret information, and contributes to the ultimate findings. Undertaken well, good qualitative research should yield rich and believable evidence (internal validity or credibility), that has relevance and utility to other people in other situations (external validity or transferability), based on research processes that can be replicated to produce similar findings (reliability or dependability).(165, 166)

The difference between a positivist approach and a relativist approach to research can be demonstrated using a tree as a simplified example. The quantitative researcher would accept the reality that the tree is a tree, regardless of who is examining it, and would aim to describe the tree by collecting objective data, e.g. the height, number of branches, presence of fruit etc. In contrast, a qualitative researcher would recognise that the tree has a greater meaning that is shaped by people's interactions with it and

would seek to explore this. The researcher may discover that the tree bears fruit that feeds the village or serves as an important landmark. The researcher themselves may have a perspective on the tree, perhaps they played beneath it in childhood.

Clearly, neither approach is “right” or “wrong”, although historically, purists considered the two methodologies to be incompatible and based on opposing research paradigms.(167) A more pragmatic standpoint recognises the merit in both methods and appreciates that multiple different descriptions can exist for the same phenomenon, with all being valid.(168) Understanding the theory behind each approach and recognising the appropriateness of each for a specific task allows the correct approach to be selected for the research that is planned. Building on this, Teddlie and Tashakkori suggested that the two approaches could be complementary and proposed an “integrationist approach”.(169) After all, in the example above, if the research aims to understand the tree in its entirety, the use of both methods is the only way to obtain a complete picture, including the tree in its objective state and its meaning to those who interact with it.

In the context of clinical trials, the addition of qualitative research methods can identify and help address potential methodological issues.(170) For a pilot or feasibility study, mixed methods can provide vital information to inform the subsequent full-scale trial that could not be obtained from quantitative data alone. Previous qualitative research undertaken alongside RCTs has revealed modifiable barriers to participant enrolment, including understanding of randomisation, willingness to receive the allocated intervention and appreciation of clinician equipoise.(170, 171) In one longitudinal MPM

study, semi-structured interviews were undertaken with participants in the pilot phase of a surgical trial that was perceived as difficult to recruit to.(172) The results highlighted the challenges of communicating complex information about research trials to patients and emphasised the importance of maintaining equipoise when describing treatment options. Having been informed by the qualitative data, the subsequent full-scale trial has consistently recruited above target.

There are several techniques for combining quantitative and qualitative research, which vary depending on the emphasis placed on each method, the chronology of the research and the timing and strategy of combining the findings.(168) In this doctoral work, the qualitative content of Workstream 4 was embedded within the feasibility trial of Workstream 3, with equal weight placed on the two methodologies. The qualitative data was analysed contemporaneously with direct interaction on the trial, as well as being integrated with quantitative outcomes at the end of the trial, based on a parallel, concurrent, interactive model with subsequent convergence.(173) This approach, shown graphically in Figure 1.6, allows simultaneous implementation of qualitative and quantitative methods, with the former directly influencing the latter, before the results of both are mixed to provide an overall interpretation.

Participants took part in qualitative interviews on completion of the 12-week trial period. The interviews explored their experiences of participation and aimed to gain insight into their views about trial design and specific research processes, including acceptability. If a qualitative theme was identified relating to a particular element of the trial and if that element could be changed without affecting the scientific quality of the

trial, the protocol was adapted in light of the qualitative finding. Once the trial finished, the qualitative findings were integrated with the quantitative results to create an overall assessment of whether the trial was feasible and acceptable to participants and their relatives. The qualitative results were also used to identify what elements of the trial were not acceptable and how they could be changed or improved for future trials.

Previous qualitative research in patients with MPM highlighted that people with the condition tended to be stoical in relation to their symptoms and the terminal nature of the disease.(174) In contrast, relatives and family members were often more vocal, especially about the emotional and practical burden of the disease and, as a result, tended to act as advocates on behalf of the patients. For this reason, relatives and carers of trial participants were also invited to take part in qualitative interviews to ascertain their views on trial participation and overall impact on their family member.

1.5.4. Co-production and patient & public involvement

The methods and resources used during this thesis, specifically in Workstreams 3 and 4 were chosen and developed using co-production techniques with input from a dedicated patient and public involvement (PPI) group. This ensured that the research was informed by a range of perspectives and benefitted from a combination of different knowledge and skills, including those of the people at the heart of the research, i.e. people with MPM.(175) Co-production was a dynamic process, with regular dialogue between the study team and members of the PPI group, supported by resources obtained from NIHR's INVOLVE network.

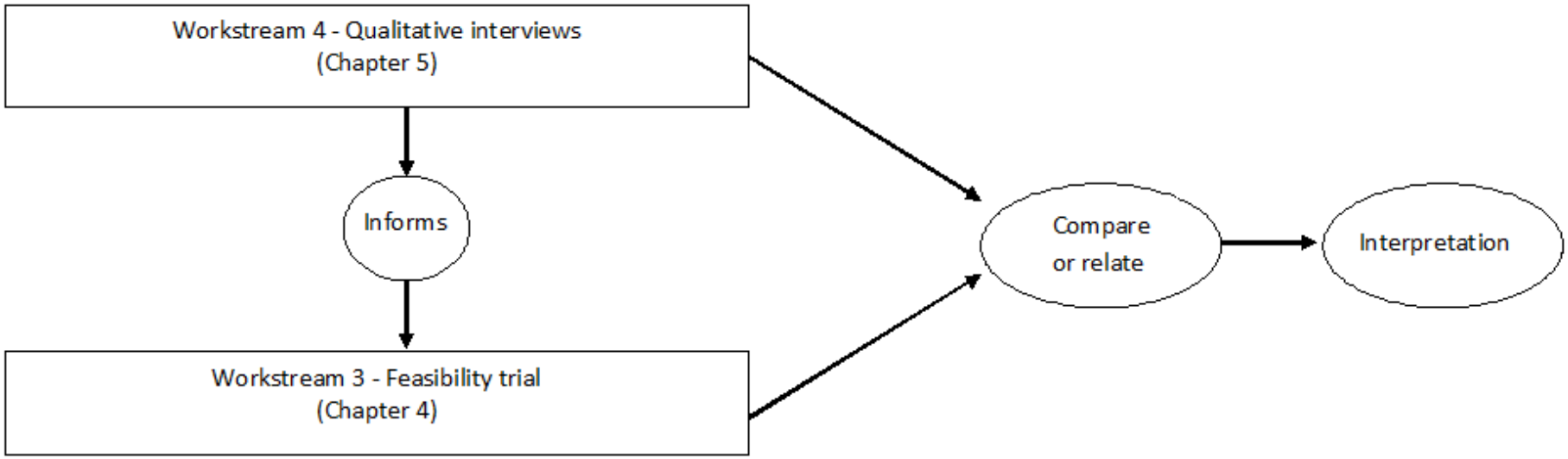


Figure 1.7 Mixed methods research design – a parallel, concurrent, interactive model with subsequent convergence. Adapted from Creswell, JW and Plano Clark, VL. Chapter 3. Choosing a Mixed Methods Design. Designing and conducting mixed methods research.(173)

Chapter 2 - A systematic review of intrapleural bacterial products in pleural malignancy

The work in this chapter has been published:

Bibby AC, Walker S & Maskell NA. Are intra-pleural bacterial products associated with longer survival in adults with malignant pleural effusions? A systematic review. *Lung Cancer* 2018: 122:249-256.(176)

ACB devised the concept and designed the study, developed and performed the literature search, screened abstracts and full-text articles for inclusion and performed data extraction. ACB also evaluated included studies for risk of bias, analysed pooled study data and wrote the first draft of the paper. SW was the second reviewer of abstracts and full-text papers, and independently performed data extraction. NAM assisted with development of the study idea and design, resolved any disagreements between the independent reviewers and reviewed the final analysis. All authors reviewed and refined the paper prior to publication.

2.1. Background

As described in Chapter 1, bacterial products have been used intra-pleurally for decades to induce pleurodesis in patients with MPE. Several researchers and clinicians postulated that they exerted additional, anti-tumour effects via cytokine release and induction of effector immune cell responses.(84-90) However, the research focus has always been on the efficacy of these products to control pleural fluid and no RCT has been undertaken with survival as the primary endpoint.

More recently, the anti-cancer activity of several alternative intra-pleural bacterial products has been studied in stand-alone, early phase clinical trials of patients with MPE. These trials yielded encouraging results, but the small participant numbers and methodological limitations inherent to early phase trials limited their interpretation.(94-96)

Whilst patients with MPM were included in some of these studies, none have specifically examined the effect of the products in MPM. For the reasons outlined in Chapter 1, there is a strong scientific rationale for investigating bacterial products in MPM. Prior to undertaking the proposed work in this thesis, a systematic review was performed to evaluate and summarise the existing evidence on the anti-tumour effect of intra-pleural bacterial products in MPE, including MPM.

2.2. Methods

The aim of the systematic review was to answer the question "Are intra-pleural bacterial products associated with longer survival in adults with MPE?" The review was registered on PROSPERO International Prospective Register of Systematic Reviews, registration number 50867. A summary of the protocol is available at https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017058067.

2.2.1. PICOS criteria

Systematic reviews of quantitative data, particularly those involving clinical trials, are often based on pre-specified PICOS criteria:

- **P** – Population
- **I** – Intervention
- **C** – Comparators
- **O** – Outcomes
- **S** – Study design

For this systematic review, the population of interest was adults with MPE. The intervention was intra-pleural administration of any bacterial preparation, including live or attenuated whole organisms, bacterial toxins or antigens, and bacterial cell components. Comparators included no treatment, alternative non-bacterial intra-pleural agents or placebo. The outcomes of interest were anti-cancer activity, primarily overall survival, but studies that reported 1-year survival rates, tumour response rates and adverse events were also included. Control of MPE and pleural fluid response rates were not included as outcomes, as these have been covered in a recent Cochrane systematic review and meta-analysis.(83) RCTs and non-randomised comparative studies were included.

Based on these PICOS criteria, the systematic review aimed to assess and summarise survival outcomes following administration of an intra-pleural bacterial product compared with other intra-pleural treatments, placebo or no treatment in adults with MPE.

2.2.2. Study selection

Research papers in all languages were included. Foreign language papers were translated into English using an online translation service. No date limitations were placed on the search. Studies where no abstract was available were excluded. Where clinical trial registers suggested a trial had been completed but not reported, the authors were contacted and asked to provide the data. The full eligibility criteria for studies included in the systematic review are presented in Table 2.1.

2.2.3. Data sources and search strategy

An electronic literature search was undertaken using the following databases:

- MEDLINE (1946 to 2017 week 09)
- EMBASE (1974 to 2017 week 09)
- Cochrane Database of Systematic Reviews
- Cochrane CENTRAL Register of Controlled Trials
- International Clinical Trials Registry (ISRCTN)
- EU Clinical Trials Register
- US NIH Clinical Trials Register
- Open Grey (System for Information on Grey Literature in Europe – SIGLE).

Once the electronic search was complete, a manual search was undertaken to review the references of included papers and systematic reviews to ensure no relevant papers had been missed.

	Inclusion criteria	Exclusion criteria
Participants	• Age ≥ 18 years. • Malignant pleural effusions due to any underlying tumour. • Can include mixed malignant and non-malignant effusions if results reported separately. • Can include pleural, pericardial and peritoneal effusions if results reported separately.	• Age < 18 years. • 'Operable' lung cancer. • Non-malignant pleural disease or mixed populations where results are not reported separately.
Intervention	Intrapleural delivery of a bacterial preparation, including: • Corynebacterium • BCG • Staphylococcus superantigen • Lactobacillus • LC8019 • OK432 • Lipopolysaccharide • Pseudomonas. Combination therapy with other concurrent treatments delivered via any route.	• Intravenous, intra-dermal, sub-cutaneous delivery of bacterial products. • Viral vectors for gene therapy. • Vaccine therapy. • Passive immunotherapy (i.e. primed immune cells, cytokine therapy) • Synthetic agents e.g. monoclonal antibodies.
Comparison	• Any other intra-pleural agent • No intra-pleural treatment • Placebo	
Outcome	• Survival (overall or rates at specific time points). • Tumour response rates. • Adverse events.	• Pleurodesis or pleural fluid response rates only.
Study type	• Any language • Full-text article • Randomised controlled trials • Case control studies • Comparative cohort studies • Cohort studies with historic control groups.	• Studies without a comparison group. • Early phase clinical trials. • Case series/case reports. • Review articles. • Letters/ editorials/ commentaries. • Conference abstracts. • Animal studies/ in vitro lab studies. • Studies with no abstract available.

Table 2-1 Eligibility criteria for systematic review based on PICOS criteria

The search strategy was developed with support from an information scientist at the University of York and is shown in Appendix A. The strategy included exploded MeSH headings for MPE, combined with keyword or title word searches for intra-pleural bacteria, immunotherapy and specific products. The initial search was run on 27th February 2017, with the manual search completed on 3rd March 2017. The search was repeated on 22nd February 2018, prior to publication of the systematic review, to identify any studies published in the intervening year.

2.2.4. Data extraction and risk of bias assessment

The titles and abstracts of all studies identified by the search were screened for relevance by myself (Dr Anna Bibby, AB) and by a second, independent reviewer (Dr Steve Walker, SW). Studies were included in the review if they met the eligibility criteria for the PICO variables, as stated above. Potentially eligible studies were obtained in full-text format and further screened by the reviewers, independently. Discrepancies between the reviewers were resolved by discussion, or if resolution could not be reached, by consultation with a third party (Prof Nick Maskell, NM).

Data were extracted from eligible studies by the two independent reviewers (AB and SW). If a study stated in its methodology that data relevant to the PICO criteria was collected but did not report this data in the results section, the authors were contacted and asked to provide the data.

Randomised trials that met the inclusion criteria were evaluated using the Cochrane tool for assessing risk of bias, whilst non-randomised studies were assessed using the Risk Of

Bias In Non-randomised Studies of Interventions (ROBINS-I).(177, 178) With the Cochrane tool, risk of bias was assessed over the pre-specified domains of random sequence generation, concealment of allocation, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective reporting and other potential sources of bias. Domains were judged to be at high, low or unclear risk of bias. Using ROBINS-I, risk of bias was assessed in relation to confounding, selection of participants, classification of intervention, adherence to intended intervention, missing data, measurement of outcomes and reporting of results. Studies were deemed to be at low, moderate, serious or critical risk of bias in each of these areas, or not to have sufficient information available to assess. Risk of bias was assessed independently by the same two reviewers (AB & SW), with differences of opinion resolved by discussion or involvement of a third party (NM).

2.2.5. Data synthesis and analysis

Where possible, raw data was extracted from studies to calculate the outcomes of interest i.e. overall survival, 1-year survival rates and tumour response rates. Overall survival was calculated using time-to-event analysis (Cox proportional hazards model) to generate a hazard ratio for mortality, with 95% CI. Proportional outcomes (i.e. rates) were calculated as OR with 95% CI.

Meta-analysis was planned if two or more RCTs with the same outcome were identified. Heterogeneity would be assessed visually with Forest plots and quantitatively using the I^2 statistic.(179) Since heterogeneity was expected to be high, a random effects model

was expected to be required. Ultimately, however, meta-analysis was not possible, due to variable reporting of outcomes and high heterogeneity between studies.

Univariable meta-regression and Fisher's exact test were used to explore the relationship between the likelihood of the study reporting a positive effect and study design; year of publication; patient population; and bacterial product.

2.3. Results

2.3.1. Study selection

Results of the search are shown in Figure 2.1, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.(180) Six hundred and thirty-one articles were identified by the search, once duplicates had been removed. Of these, six hundred and two were excluded at screening. Fifteen manuscripts were excluded at full-text review, for the following reasons: full-text was unavailable for five; survival outcomes were not reported or not reported separately in six; two publications reported duplicate data (the paper with the least amount of data was excluded); one article had no data on pleural effusions and one manuscript was a review article. Further information on excluded papers is shown in Appendix 2. In total, fourteen studies were included in the final review.

2.3.2. Characteristics of included studies

Of the fourteen included papers, eight were RCTs,(84, 94, 96, 101-104, 181) and six were non-randomised comparison studies,(90, 95, 122, 123, 182, 183) most commonly cohort studies with historic comparators. Studies were published between 1979 and

2007. The most frequent population was patients with MPE due to lung cancer (all sub-types),(94, 96, 122, 123, 181) or NSCLC specifically.(95, 101-103, 183) Other studies included patients with MPE due to any underlying tumour,(84, 90) MPE due to MPM,(182) and MPE secondary to lung and gastrointestinal tumours.(104) Study characteristics of RCTs and non-randomised studies are shown in Tables 2.2 and 2.3 respectively.

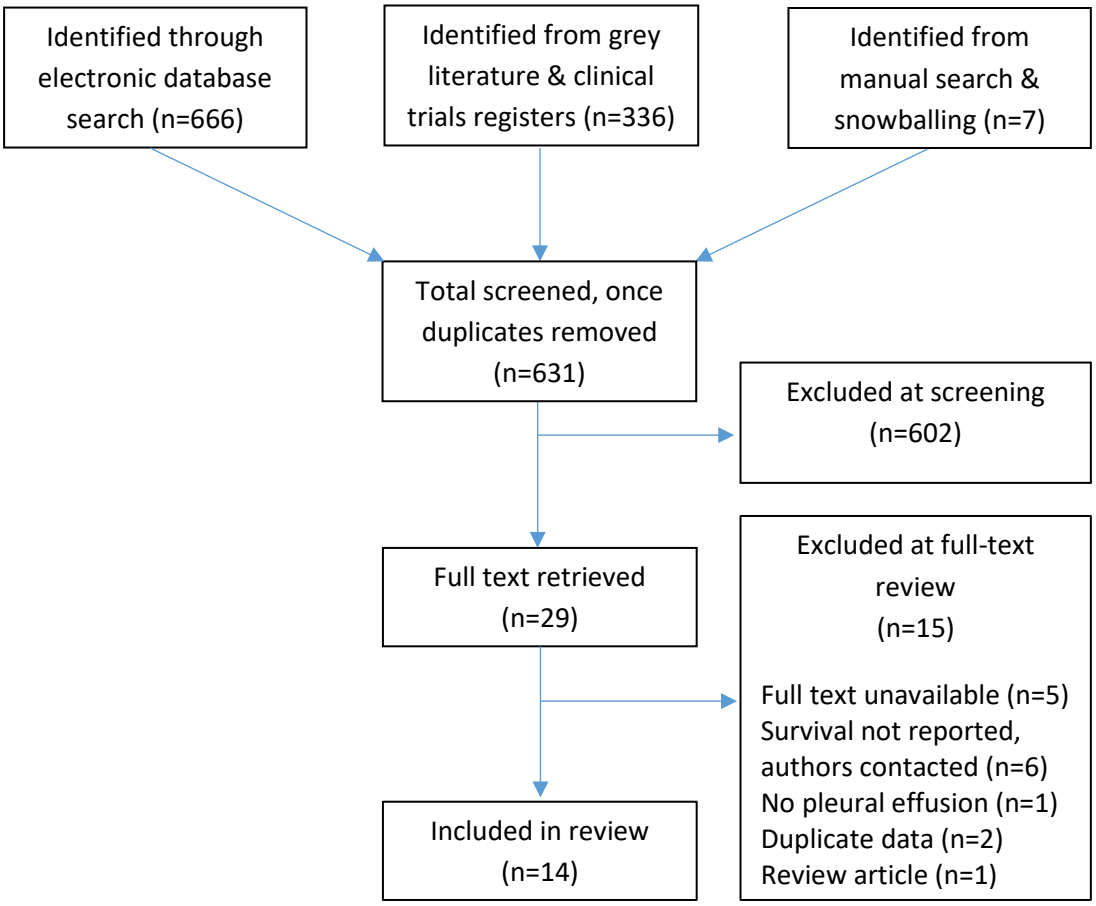


Figure 2.1 Result of search, content screening and full-text review of papers investigating intra-pleural bacterial products in malignant pleural effusion

Authors	Publication date	N	Study population, MPE 2° to:	Intervention (dose)	Comparator (dose)	MST intervention, days (95% CI*)	MST comparator, days (95% CI*)	P value
Ishida et al (101)	2006	49	NSCLC	OK423 (5KE)	Cisplatin alone (50mg)	131	152	p=0.55
				OK432 (5KE) + cisplatin (50mg)		256		
Kasahara et al (103)	2006	40	NSCLC	OK432 (10KE)	OK432 (1KE)	235	158	Not reported
Luh et al (96)	1992	55	Lung cancer	OK432 (10KE)	Mitomycin C (8mg)	177	156	NS
Yoshida et al (102)	2007	105	NSCLC	OK432 (0.2KE/kg)	Bleomycin (1mg/kg)	337 (186.9–408.8)	225 (151.2-265.3)	NS
					Etoposide (80mg/m^2) + cisplatin (80mg/m2)		320 (240.8-399.7)	
Nio et al (104)	1999	42	Lung or GI cancer	OK432 (1-10KE)	I/V and I/P chemotherapy (various)	51	74	p=0.530
				OK432 (1-10KE) + I/P chemotherapy (various)		115		p=0.080
Masuno et al (94)	1991	95	Lung cancer	*Lactobacillus casei* (0.2mg) + doxorubicin (40mg)	Doxorubicin alone (40mg)	232	125	p=0.0061
Millar et al (84)	1980	21	Any tumour	*C. Parvum* (7mg)	Mustine (20mg)	80 (mean)	86 (mean)	NS
Yamamura et al (181)	1983	68	Lung cancer	*Nocardia rubra* (400mcg) + doxorubicin (40mg)	Doxorubicin alone (40mg)	266	190	p<0.05

Table 2-2 Summary of randomised trials included in the systematic review (nb all agents were delivered intra-pleurally unless otherwise stated)

Abbreviations: 95% CI – 95% confidence intervals; C. Parvum – Corynebacterium parvum; GI – gastrointestinal; HR – hazard ratio; I/P – intra-pleural; I/V – intravenous; KE – Klinische Einheit; kg – kilogram; mcg – microgram; mg – milligram; MST – median survival time; MPE – malignant pleural effusion; NS – non-significant; NSCLC – non-small cell lung cancer

**where reported*

Authors	Publication date	Study design	Study population, MPE 2° to:	N	Intervention (dose)	Comparator (dose)	MST intervention, months (95% CI*)	MST comparator, months (95% CI*)	P value
Ren et al (95)	2004	Case series with historic controls	NSCLC	32	*Staph aureus* Superantigen (100-400 mcg)	Talc	7.9 (5.9-11.4)	2.5 (1.3-3.4)	p=0.044
McLeod et al (90)	1985	Cohort with historic controls	Any tumour	67	*C. Parvum* (7mg)	Mustine (20mg)	8.2 (mean)	3.9 (mean)	p<0.01
Senyigit et al (182)	2000	Case series	MPM	138	*C. Parvum* (7mg)	Oxytetracycline (35mg/kg)	10	11	NS
						Nitrogen mustard (0.4mg/kg)		9	
Shimizu et al (183)	2005	Retrospective case control	NSCLC	32	OK432 (dose not stated)	Cisplatin (80mg/m2)	14	18	NS
Yamamura et al (123)	1979	Cohort with historic controls	Lung cancer	87	BCG cell wall skeleton (200-400mcg)	Usual treatment	10	6	p=0.016
Yasumoto et al (122)	1979	Cohort with historic controls	Lung cancer	30	BCG cell wall skeleton (5mg) + chemotherapy	Usual treatment	8** (6.2-18.2)	4** (3.9-7.0)	p=0.016

Table 2-3 Summary of non-randomised studies included in the systematic review (nb all agents were delivered intra-pleurally unless otherwise stated)

Abbreviations: 95% CI – 95% confidence intervals; C. Parvum – Corynebacterium parvum; GI – gastrointestinal; HR – hazard ratio; I/P – intra-pleural; I/V – intravenous; KE – Klinische Einheit; kg – kilogram; mcg – microgram; mg – milligram; MST – median survival time; MPE – malignant pleural effusion; NS – non-significant; NSCLC – non-small cell lung cancer.

**Where reported **Calculated by the author of this thesis*

Different bacterial products were used, including OK432 in six studies,(96, 101-104, 183) *Corynebacterium parvum* in three,(84, 90, 182) BCG cell wall skeleton in two,(122, 123) and *Lactobacillus casei*,(94) *Staphylococcus aureus* superantigen,(95) and *Nocardia rubra* cell wall skeleton(181) in one apiece. Comparators included intra-pleural chemotherapy,(84, 90, 94, 96, 101, 102, 104, 181, 183) usual treatment,(122, 123) talc poudrage,(95) or alternative pleurodesis agents(182). One RCT compared two different doses of the same bacterial product.(103) Two studies employed a three-arm design, comprising bacterial product alone, chemotherapy alone and bacteria/chemotherapy combination.(101, 104)

2.3.3. Risk of bias assessment

Risk of bias was high or unclear in at least one domain for all eight randomised trials included in the systematic review (Table 2.4). Half the RCTs were published prior to the development and publication of the Consolidated Standards of Reporting Trials (CONSORT) guidance in 1996, and much of the information required to assess risk of bias was missing.(184) Information on random sequence allocation and concealment of allocation was provided in only three trials, whilst information on blinding of participants and outcome assessments was lacking in all but two. Selective reporting and incomplete outcome data were commonplace, with only three RCTs including all participants in the final analysis and reporting all the outcomes stated in the methodology.

All non-randomised studies were at high risk of confounding, with several using historic controls or patient groups with differing baseline characteristics (Table 2.5). Selection

bias was also a risk for non-randomised studies, with many failing to state how eligible participants had been identified or selected. Description of the intervention and adherence to it was relatively well reported, however outcome measures were frequently not pre-stated, not defined or not assessed by blinded assessors.

Individual studies and their limitations are described in sections 2.3.5 for RCTs and 2.3.6 for non-randomised studies.

	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other
Ishida et al (101)							
Kasahara et al (103)							
Luh et al (96)							
Yoshida et al (102)							
Nio et al (104)							
Masuno et al (94)							
Millar et al (84)							
Yamamura et al (1983) (181)							

Table 2-4 Risk of bias assessment for randomised trials included in the systematic review, assessed using Cochrane Risk of Bias Tool. Red = high risk of bias, green = low risk of bias, yellow = unclear risk of bias.

	Confounding	Selection of participants	Classification of intervention	Deviation from intervention	Missing data	Outcome measurement	Reporting of result
Ren et al (95)							
McLeod et al (90)							
Senyigit et al (182)							
Shimizu et al (183)							
Yamamura et al (1979) (123)							
Yasumoto et al (122)							

Table 2-5 Risk of bias assessment for non-randomised studies included in the systematic review, assessed using ROBIN-I Tool. Black = critical risk of bias, red = serious risk of bias, yellow = moderate risk of bias, green = low risk of bias, grey = no information.

2.3.4. Synthesis of results

Six of the fourteen included studies reported an overall survival benefit associated with intra-pleural bacterial immunotherapy.(90, 94, 95, 122, 123, 181) This ranged from a median survival benefit of 2.5 to 5.4 months from the date of drug administration. However, limited reporting of confidence intervals meant that the precision of most estimates could not be evaluated. The remaining eight studies demonstrated no difference in survival between patients treated with intra-pleural bacteria and comparators.(84, 96, 101-104, 182, 183)

Only two papers provided measures of variance for the survival estimate, specifically 95% CI.(95, 102) One paper provided patient-level data, and I performed survival analysis using this data.(122) No other measures of variance were available and requests for raw data were unsuccessful, therefore meta-analysis was not possible. Additionally, heterogeneity within and between populations, interventions and comparators meant meta-analysis was inappropriate, even using a random-effects model, as a pooled effect estimate would not be applicable to specific populations or products. Consequently, narrative synthesis was undertaken.

2.3.5. Results of individual studies – randomised trials

Five RCTs investigated OK432, a heat- and penicillin-killed *Streptococcus pyogenes* preparation. An initial dose-finding trial found that 10 Klinische Einheit (KE) of OK432 was associated with longer survival than a dose of 1KE (33.6 weeks vs 22.6 weeks) but interpretation of these results was difficult without a non-OK432 comparator group.(103)

Other trials compared OK432 with intra-pleural chemotherapy. The most methodologically reliable was a three-armed study that compared OK432 at a dose of 0.2KE/kg with two different intra-pleural chemotherapy regimens in MPE due to NSCLC.(102) No survival difference was seen across the three groups. Similarly, Luh et al found no difference in survival between lung cancer patients treated with intra-pleural mitomycin C or OK432 (10KE).(96) However, this paper was at risk of reporting bias as outcomes were not stated a priori and some participants were excluded from the analysis due to early death.

Ishida et al reported a trend towards longer survival in patients with MPE secondary to NSCLC treated with OK432 in a three-armed trial that compared 5KE of OK432 plus intra-pleural cisplatin with OK432 alone or cisplatin alone.(101) Median survival was 8.3 months in the combination arm, compared with 5 months for cisplatin and 4.3 months for OK432 alone. Statistical significance was not achieved (p=0.55), however, the trial was underpowered with just 49 participants – a sample size that was based on time constraints rather than a formal calculation.

The final study to evaluate OK432 compared multiple regimens of intra-venous and intra-pleural chemotherapy with varying doses of OK432, either alone or in combination with intra-pleural chemotherapy.(104) The heterogeneity of interventions made interpretation difficult, and the use of an comparator with a proven survival benefit (intravenous chemotherapy) in one arm must be taken into account when considering the results. No survival difference was seen between the arms, however the combination of OK432 and intra-pleural chemotherapy was associated with longer survival compared with OK432 alone (115 days vs 51 days). Given survival was similar for people treated with OK432 and patients treated with intra-venous chemotherapy, the study could be interpreted to mean intra-pleural OK432 is as effective as standard of care chemotherapy. However, the study was not designed as a non-inferiority trial and the absence of measures of variance for the survival estimates prevented meaningful interpretation.

Yamamura et al also combined intra-pleural chemotherapy with a bacterial product, using *Nocardia rubra* cell wall skeleton in conjunction with doxorubicin *versus* doxorubicin alone in 68 participants with MPE secondary to lung cancer.(181) The *nocardia* group had a median survival of 266 days, compared with 190 days for single-agent doxorubicin ($p<0.05$). However, patients who died within 30 days of randomisation were excluded from the analysis, risking attrition bias. Furthermore, this outcome was the result of a sub-group analysis of data from a larger trial in which multiple analyses were undertaken, without pre-specification in the analysis plan. Therefore there is a risk of multiple testing and of reporting bias.

Another RCT randomised 95 participants with lung cancer MPE to receive intra-pleural *Lactobacillus casei* and doxorubicin or doxorubicin alone.(94) Patients who received *Lactobacillus* had a median survival of 232 days compared with 125 days in controls ($p=0.0061$). However, 19 patients were excluded from the final analysis, creating a high risk of attrition bias. Interestingly, no further trials were undertaken using either *Lactobacillus casei* or *Nocardia rubra* despite these positive results.

The final RCT investigated *Corynebacterium parvum*, randomising 21 participants to either *Corynebacterium* or intra-pleural mustine.(84) No survival difference was seen in this small study, with mean survival of 80 days for *Corynebacterium* and 86 for mustine. No information was provided about the distribution of the data, so it is unclear whether use of mean survival values was appropriate. Additionally, outcomes were not specified a priori, creating a risk of reporting bias.

2.3.6. Results of individual studies – non-randomised studies

Two non-randomised studies evaluated BCG cell wall skeleton (BCG-cws) alongside standard care in patients with lung cancer.(122, 123) The first reported median survival of 10 months in 55 patients treated with BCG-cws, compared with 6 months in 32 age-matched historic controls (p=0.016).(123) The second presented patient-level data for 13 patients with MPE given BCG-cws and 17 historic controls.(122) These data were analysed to reveal median survival of 8 months in the BCG-cws group and 4 months in controls, with a hazard ratio of 0.374 (95% CI 0.168-0.833, p=0.016). However, it was unclear how participants were selected for these studies, and the latter included a greater proportion of women in the BCG-cws group, a factor known to be associated with longer survival in lung cancer.(185) Additionally the use of historic controls may have introduced confounding due to potential advances in care between the two time periods.

Two observational studies investigated *Corynebacterium parvum*.(90, 182) McLeod et al retrospectively analysed data from 67 patients with MPE treated with *Corynebacterium parvum* or intra-pleural mustine at a single UK centre.(90) Mean survival was 251 days in the *Corynebacterium* group compared with 119 days in the mustine group (p<0.01). However, 14 patients died within 30 days of treatment and were excluded from the final analysis, introducing potential bias for survival outcomes. Additionally, patients who received mustine were treated prior to 1980, whilst the majority of *Corynebacterium* patients were treated after this, raising the possibility of temporal confounding. Furthermore, 6 patients who failed pleurodesis with mustine were excluded from the analysis, generating potential bias due to differential attrition.

Senyigit et al also investigated *Corynebacterium parvum*, but in patients with MPM.(182) They described 117 patients who received intra-pleural *Corynebacterium*, oxytetracycline or nitrogen mustard. No survival difference was detected between the three groups, with mean survival of 10 months in *Corynebacterium* patients, 11 months in oxytetracycline patients and 9 months in patients treated with nitrogen mustard. The study was at risk of attrition bias as 21 participants were excluded from the final analysis due to death, disease progression or loss to follow up. In addition, time-to-event modelling was not employed for survival analysis and thus censored data was not taken into account.

Shimizu and colleagues evaluated 32 patients with NSCLC treated with either intra-pleural OK432 or cisplatin between 2000 and 2004.(183) They found no difference in mortality, with median survival of 14 weeks in OK432 patients and 18 weeks in the cisplatin cohort. However, the two groups were markedly dissimilar, with worse prognostic characteristics in the OK432 group and less systemic chemotherapy administered to these patients. These differences could have attenuated a potential survival benefit associated with OK432, although the lack of observed survival difference is consistent with previous RCT data.(96, 101-104)

Finally, Ren and colleagues gave intra-pleural *staphylococcus* superantigen (SSAg) to 14 patients with MPE secondary to NSCLC, six of whom also received intra-venous SSAg. Outcomes were compared with 18 historic controls from up to 10 years earlier. Median survival was 7.9 months in SSAg patients, compared with 2 months in controls

(p=0.0023), leading the authors to conclude that SSAg had anti-neoplastic effects. However, the study was vulnerable to a number of confounding factors, mainly relating to the differences between the two treatment groups. As well as the temporal divide between cases and controls, controls were treated in the USA whilst cases were recruited and treated in Japan. Differences in epidemiology, tumour and population genetics, healthcare systems, and treatment approaches between the 2 countries mean the population are unlikely to be comparable.

2.3.7. Meta-regression

More non-randomised studies reported favourable survival with bacterial products than RCTs (4/6; 66.7% vs 2/8; 25%) but the relationship was not confirmed by meta-regression (OR 0.17, 95% CI 0.16-1.72, p=0.132). A greater number of studies published prior to 1996, i.e. before the first iteration of the CONSORT reporting guidelines were produced, were positive compared with studies published after that date (6/8; 75% vs 1/6; 16.7%). Meta-regression supported this association (OR 15, 95% CI 1.03-218.3, p=0.047), albeit with an imprecise estimate of the relationship due to the small number of studies. Studies involving lung cancer patients were more likely to be positive (4/6; 66.7%), compared to studies of MPE secondary to NSCLC (1/5; 20%), any tumour (1/2; 50%) or MPM (0/1; 0%) but regression analysis did not demonstrate a convincing association (OR 0.47, 95% CI 0.18-1.21, p=0.116).

No specific bacterial product appeared more effective, although patients treated with *Lactobacillus casei* and *Nocardia rubra* had longer survival in two respective RCTs, whilst BCG cell wall skeleton was associated with a four-month extension to median survival in

both non-randomised studies that utilised it.(94, 122, 123, 181) OK432 was associated with no survival benefit in 5 RCTs and 1 non-randomised study,(96, 101-104, 183) although in one of those studies the comparator was intra-venous chemotherapy, i.e. standard care.(104) *Corynebacterium* parvum was associated with longer survival in one non-randomised study,(90) but no effect in 2 others (1 randomised and 1 non-randomised),(84, 182) whilst *Staphylococcus* aureus superantigen was associated with longer survival in a single observational study.(95)

2.4. Summary of findings

The existing evidence was mixed regarding the potential survival benefits associated with intra-pleural bacterial products in pleural malignancy. All eligible studies were of low quality and were at high or unclear risk of bias in at least one domain. Synthesis of data was limited due to the heterogeneity of bacterial products, underlying diseases and outcome measures studied. Additionally, few studies presented measures of variance, which precluded meta-analysis.

There is, therefore, no reliable evidence at present to support the use of intra-pleural bacterial products to prolong survival in pleural malignancy. Well-designed, suitably powered RCTs are needed, but choosing the appropriate bacterial product and target population is likely to prove challenging.

Chapter 3 – A population-level cohort study examining the association between pleural infection and survival in mesothelioma

The work described in this chapter has been published:

Bibby AC, de Fonseka D, Carslake DJ & Maskell NA. Is pleural infection associated with longer survival in mesothelioma? A population-based cohort study using data from Hospital Episode Statistics. *Cancer Epidemiology* 2019;59:75-82.

ACB conceived the study, designed the methodology, cleaned & analysed the data, interpreted the results and wrote the manuscript. DDF helped refine the methodology, assisted with data analysis and contributed to manuscript writing. DJC developed the statistical analysis plan, assisted with data analysis, interpreted the results and helped write the manuscript. NAM developed the study concept, reviewed the analysis plan, assisted with interpretation of results and refined the manuscript.

3.1. Background

Whilst the evidence for directly administered intra-pleural bacterial products is limited in malignant pleural disease, bacteria can also occur spontaneously in the pleural space as a result of pleural infection. Small studies have reported longer survival in patients with malignancy who developed pleural infection, although the majority of these were in patients who had undergone curative surgical resection of lung tumours and were theoretically cancer-free at the point of developing pleural infection.(159-161) In mesothelioma, a single observational study reported longer survival in people who

developed pleural infection with an IPC in situ, compared with those without infection.(186) Patient numbers were small, however, and confidence intervals wide, such that the true mortality benefit may have been extremely small and, therefore, not clinically relevant.

This study was designed to investigate whether pleural infection was associated with survival in mesothelioma, using a national clinical dataset. This would inform the overall thesis hypothesis regarding bacteria in the pleural space and survival in mesothelioma.

3.2. Methods

3.2.1. Study Design

This was a population-based cohort study using historic data from Hospital Episode Statistics (HES) linked to Office of National Statistics (ONS) mortality data. The research was approved by the Proportionate Review Sub-Committee of the National Research Ethics Committee London – Central (14/LO/1258).

3.2.2. Study population & data sources

The study population consisted of all patients with mesothelioma seen in a hospital in England between 01/01/2005 and 31/12/2014. Participants were identified from HES, a database containing details of every hospital stay, emergency attendance and outpatient appointment in NHS hospitals in England. All episodes containing an International Classification of Diseases Tenth Edition (ICD-10) code for mesothelioma (i.e. C45, C45.0, C45.1, C45.2, C45.7 or C45.9) during the study period were extracted. Patients whose first recorded episode with a mesothelioma code occurred prior

01/01/2005 were excluded, as were patients whose recorded address was outside England, as HES would not have information for the majority of their hospital attendances. Episodes of pleural infection were identified within the cohort using ICD-10 codes J86, J86.0 and J86.9. Information on additional study variables were obtained from HES.

The extracted mesothelioma cohort was linked to ONS mortality data for the period 01/01/2005 to 28/03/2016, using individual, pseudonymised patient identifiers. ONS contains information taken from death certificates for all deaths registered in England and Wales.

3.2.3. Exposure variables

The exposure variable was an episode of pleural infection occurring during the study period. The date of pleural infection was recorded as the earliest date of the first episode in which pleural infection was recorded. If a participant experienced more than one episode of pleural infection, the earliest episode was used.

3.2.4. Outcome variables

The primary outcome was survival, defined as date of diagnosis with mesothelioma to date of death. Date of diagnosis was defined as the start date of the earliest episode where mesothelioma was recorded. Date and cause of death were obtained from death certificates. Patients with zero survival time and death certificate diagnoses of mesothelioma were excluded from the analysis.

3.2.5. Confounding/mediator variables

Patient variables and treatment details were extracted from HES, using ICD-10 and Office of Population Censuses and Surveys Classification of Interventions and Procedures (OPCS-4) codes. Confounders were defined as variables that had a potential influential effect on the risk of pleural infection and on survival. Confounders included sex, age at mesothelioma diagnosis, disease site (pleural; peritoneal; pericardial; other or unspecified), socio-economic status based on index of multiple deprivation (IMD) quintile (1=least deprived; 5=most deprived), rural/urban classification (urban area of population >10000; town or fringe; village; hamlet or isolated dwelling), comorbidities (defined as number of additional diagnostic codes at initial presentation), mode of initial attendance (outpatient appointment; inpatient admission; procedure or operation), year of diagnosis (before or after 01/01/2008), documented asbestos exposure, documented pleural plaques, and binary (yes/no) outcomes for whether the patient had undergone a biopsy, a thoracoscopy (where a fibreoptic camera in inserted into the pleural space, either under sedation and local anaesthesia or as a surgical operation) or a pleurodesis procedure (where a chemical irritant, usually talc, is introduced in to the pleural space either as a slurry via a chest drain or as poudrage during thoracoscopy).

Mediators were classified as variables that were located on the causal pathway between pleural infection and survival. They included number of pleural interventions, average number of hospital episodes per year, undergoing thoracic surgery and receiving chemotherapy.

3.2.6. Statistical analysis

Datasets were merged and de-duplicated to create a single record for each patient. Descriptive statistics were used to describe patient characteristics, stratified by pleural infection. Data for each variable was visually inspected. Mean values with 95% confidence intervals were calculated for normally distributed continuous data, with medians and inter-quartile ranges (IQR) used for non-parametric variables. Categorical and binary data were reported as proportions. Significance tests were performed using t-tests and Kruskal-Wallis tests for parametric and non-parametric data respectively. χ^2 tests were used for binary, ordinal or categorical variables, with Fisher's exact test employed if the expected frequency in any group was less than 10. The only variable with missing data was socioeconomic status. A separate 'missing' category was created for this variable and included in all analyses.

Pleural infection incidence rate was calculated per 1000-person years. Because the incidence of pleural infection was likely to vary depending on time since diagnosis, separate incidence rates were calculated for the periods 0-30 days, 31-90 days and 90+ days post-mesothelioma diagnosis.

Factors associated with pleural infection were investigated using time-to-event analysis using univariable and multivariable Cox proportional hazards models with time since mesothelioma diagnosis as the time axis. All variables were included in the multivariable model, regardless of significance on univariable testing. Potential interactions between pre-specified variables (comorbidities, age, IMD category, number

of pleural procedures, average number of hospital attendances per year and year of diagnosis) were tested using the Mantel Haenszel method.

Median survival was reported for the whole group, and for patients who did and did not experience pleural infection at any time after their diagnosis with mesothelioma. Kaplan Meier curves were plotted to visually compare unadjusted survival in people with and without pleural infection. Overall survival was also assessed in patients diagnosed before and after 2008, the year that pemetrexed and cisplatin chemotherapy became standard care in the UK.(187)

Survival analyses were modelled using Cox proportional hazards models, having checked the validity of the proportional hazards assumption using Schoenfield residuals and visually with "log-log" plots for individual variables. Because any potential hazard associated with pleural infection could only occur after the infection began, and due to clinical suspicion that the hazard may change following recovery from infection, pleural infection was handled as a time-varying covariable by splitting follow-up into pre-infection, ≤30 days post-infection and >30 days post-infection. Thoracic surgery and chemotherapy were also handled as time-varying covariables, with follow-up split at the time of first treatment. Survival was censored on 28/03/2016.

The primary survival model assessed all-cause mortality, with mesothelioma-specific mortality modelled as a secondary analysis, censoring participants who died of other causes on their day of death. Initially the model was adjusted for confounders alone, then the analysis was repeated to include mediators, and the impact evaluated. The

main analysis included all patients. A priori sub-group analysis investigated patients with pleural mesothelioma, since pleural infection was likely to be most relevant to these patients.

3.3. Results

22,896 patient records were identified, of whom 22,149 met the inclusion criteria and contributed 24,453 patient-years in total (Figure 3.1). In the final cohort of 22,149 patients, 81.7% were male, mean age was 71.8 years (range 18-102), and the majority had pleural mesothelioma (51.5% pleural, 5.0% peritoneal, 0.4% pericardial, 43.1% other or not specified). For 72.7% of patients, the first recorded diagnosis of mesothelioma occurred during an inpatient admission, whilst 23.5% were diagnosed at operation or procedure, and 3.8% during an outpatient appointment. The median number of comorbid codes at presentation was 5 (IQR 3-7), with essential hypertension (n=6,428; 28.9%), pleural effusion (n=5,337; 24.0%), drug, alcohol or tobacco use (n=4,269; 19.2%) and ischaemic heart disease (n=3,789; 17.1%) the most frequent.

3.3.1. Pleural infection

Of 22,149 patients, 510 (2.3%) developed pleural infection during the study period. The incidence rate of pleural infection was 21.1 per 1000 patient-years (95% CI 19.4-23.0). The incidence rate was higher in the first 30 days after diagnosis with mesothelioma (169 per 1000 patient-years, 95% CI 150.8-190.2), followed by the period between 31 and 90 days after diagnosis (34.0 per 1000 patient-years, 95% CI 27.8-41.6). Pleural infection occurred much less frequently once 90 days had passed since diagnosis (6.6 cases per 1000 patient-years, 95% CI 5.6-7.9).

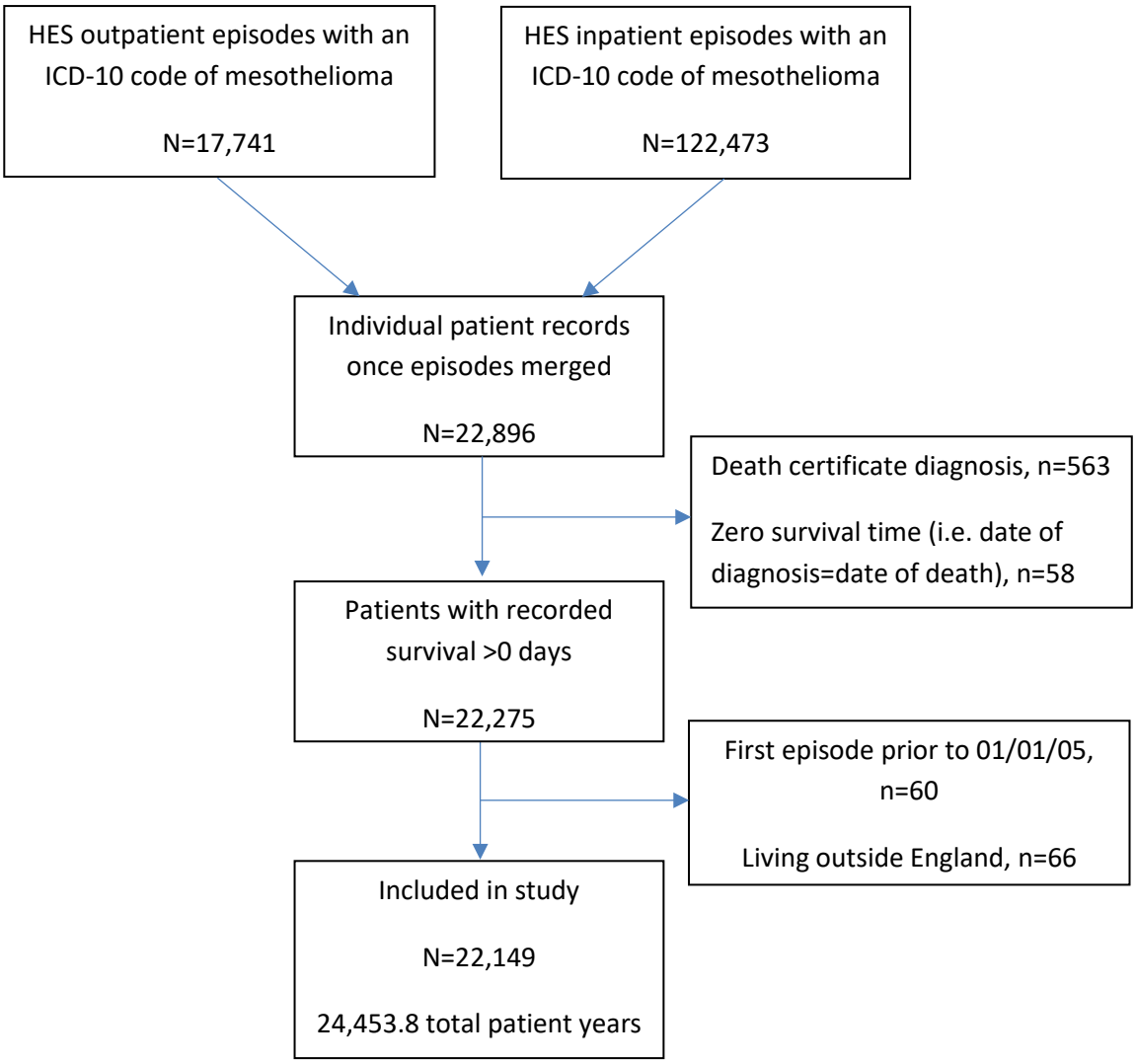


Figure 3.1 Identification of patients and eligibility screening for population-cohort study. HES – Hospital Episode Statistics

Patient characteristics are shown in Table 3-1, stratified by pleural infection. The pleural infection group had a higher proportion of men, were more likely to be diagnosed as inpatients and had more comorbidities at diagnosis. Patients with pleural infection were more likely to have undergone pleural drainage or aspiration, thoracoscopy, thoracic surgery or pleurodesis and were less likely to receive chemotherapy. Overall, patients with pleural infection underwent more pleural interventions and had a higher number of hospital episodes per year than patients without infection. Predictably, pleural infection occurred more often in people with pleural mesothelioma.

	Pleural infection N=510	No pleural infection N=21,639	p
Male, n (%)	454 (89.0)	17,638 (81.5)	<0.001
Age, mean (SD)	70.9 (9.84)	71.8 (9.93)	0.038
IMD quintile, n (%)			
1 (least deprived)	93 (18.2)	4,218 (19.5)	
2	101 (19.8)	4,192 (19.4)	
3	117 (22.9)	4,193 (19.4)	
4	100 (19.6)	4,199 (19.4)	
5 (most deprived)	93 (18.2)	4,195 (19.4)	
Missing	6 (1.2)	642 (2.9)	0.090
Rural/urban location, n (%)			
Urban with ≥10,000 population	385 (75.5)	17,079 (78.9)	
Town and Fringe	65 (12.8)	2,202 (10.2)	
Village	42 (8.2)	1,688 (7.8)	
Hamlet/ isolated dwelling	20 (3.5)	670 (3.1)	0.251
Mode of initial attendance, n (%)			
Outpatient appointment	1 (0.2)	843 (3.9)	
Inpatient admission	429 (84.1)	15,674 (72.4)	
Day case procedure/operation	80 (15.7)	5,122 (23.7)	<0.001
No. of comorbid codes, median (IQR)	6 (4-9)	5 (3-7)	<0.001
Documented asbestos exposure, n (%)	107 (21.0)	3,418 (15.8)	0.002
Documented pleural plaques, n (%)	33 (6.5)	1,164 (5.4)	0.281
Pleural interventions			
Pleural drainage/aspiration	354 (69.4)	7,659 (35.4)	<0.001
Thoracoscopy	276 (54.1)	7,595 (35.1)	<0.001
Percutaneous pleural biopsy	149 (29.2)	5,745 (26.6)	<0.001
Pleurodesis	169 (33.1)	5,925 (27.4)	<0.001
Total no of pleural procedures, median (IQR)	3 (1-4)	1 (0-2)	<0.001
Diagnosed after 2008, n (%)	311 (61.0)	13,171 (60.9)	0.959
Site of disease, n (%) Pleural	317 (62.2)	11,084 (51.2)	
Peritoneal	7 (1.4)	1,104 (5.1)	
Pericardial	0 (0)	80 (0.4)	
Other/ Not specified	186 (36.4)	9,371 (43.3)	<0.001
Average no. of hospital episodes per year, median (IQR)	3.5 (2-5.5)	3 (1.5-5)	<0.001
Treatment received, n (%)			
Chemotherapy	51 (10.0)	3,949 (18.3)	<0.001
Radiotherapy	2 (0.4)	221 (1.0)	0.254
Thoracic surgery	233 (45.7)	3,482 (16.1)	<0.001
Infection/sepsis cause of death	3 (0.6)	118 (0.6)	0.912

Table 3-1 Characteristics of 22,149 patients with mesothelioma, stratified by pleural infection. P values derived from t-tests, Kruskal-Wallis tests, χ2 test and Fisher's exact test.

Abbreviations: IMD – index of multiple deprivation; IQR – interquartile range; SD – standard deviation.

	Unadjusted analysis			Adjusted analysis*		
	HR	95% CI	p	HR	95% CI	p
Male gender	1.94	1.47 to 2.56	<0.001	1.67	1.27 to 2.24	<0.001
Age at diagnosis ≤65	1	-	-	1	-	-
66 to 70	0.86	0.66 to 1.12	0.265	0.80	0.61 to 1.05	0.102
71 to75	0.92	0.71 to 1.19	0.523	0.83	0.64 to 1.08	0.163
76 to 80	1.05	0.81 to 1.36	0.699	0.93	0.71 to 1.22	0.580
81+	0.95	0.73 to 1.24	0.727	0.80	0.60 to 1.07	0.137
IMD quintile						
1 (least deprived)	0.77	0.59 to 1.02	0.065	0.77	0.59 to 1.02	0.064
2	0.84	0.64 to 1.09	0.196	0.83	0.63 to 1.08	0.163
3	-	-	-	1	-	-
4	0.86	0.65 to 1.12	0.251	0.84	0.64 to 1.10	0.200
5 (most deprived)	0.81	0.62 to 1.06	0.130	0.77	0.58 to 1.01	0.062
Missing	0.25	0.11 to 0.56	<0.001	0.62	0.27 to 1.43	0.259
Rural/urban location						
Urban ≥10,000 population	1	-	-	1	-	-
Town and Fringe	1.31	1.01 to 1.70	0.044	1.25	0.95 to 1.63	0.107
Village	1.09	0.79 to 1.49	0.615	0.94	0.67 to 1.30	0.692
Hamlet/ isolated dwelling	1.14	0.71 to 1.83	0.580	1.04	0.64 to 1.68	0.870
Mode of initial attendance						
Outpatient appointment	0.04	0.01 to 0.25	<0.001	0.12	0.02 to 0.86	0.035
Inpatient admission	1	-	-	1	-	-
Operation/procedure	0.57	0.45 to 0.72	<0.001	0.87	0.68 to 1.11	0.262
Diagnosed after 2008	0.97	0.81 to 1.16	0.762	0.83	0.69 to 1.00	0.055
No. of comorbid codes	1.13	1.11 to 1.16	<0.001	1.13	1.10 to 1.16	<0.001
Non-pleural mesothelioma	0.67	0.56 to 0.80	<0.001	0.81	0.67 to 0.97	0.025
Documented asbestos exposure	1.40	1.13 to 1.73	0.002	0.91	0.73 to 1.14	0.410
Documented pleural plaques	1.29	0.90 to 1.83	0.162	0.90	0.63 to 1.29	0.584
Pleural interventions						
Pleural drainage/aspiration	3.80	3.14 to 4.58	<0.001	1.61	1.28 to 2.02	<0.001
Thoracoscopy	1.81	1.52 to 2.15	<0.001	0.65	0.51 to 0.83	<0.001
Percutaneous pleural biopsy	1.09	0.90 to 1.32	0.353	0.76	0.62 to 0.94	0.009
Pleurodesis	1.10	0.91 to 1.32	0.320	0.44	0.35 to 0.55	<0.001
Total no. of pleural procedures	1.50	1.44 to 1.56	<0.001	1.51	1.41 to 1.61	<0.001
No. of hospital episodes per year	1.01	0.99 to 1.03	0.329	1.01	0.99 to 1.04	0.249
Treatment received						
Chemotherapy	0.44	0.33 to 0.59	<0.001	0.60	0.43 to 0.82	0.001
Radiotherapy	0.35	0.09 to 1.39	0.134	0.42	0.10 to 1.69	0.223
Thoracic surgery	5.10	3.96 to 6.58	<0.001	2.23	1.64 to 3.02	<0.001

Table 3-2 Factors associated with pleural infection in 22,149 patients with mesothelioma, from unadjusted and adjusted Cox proportional hazards models. All listed variables were included in the multivariable model.

Abbreviations: CI – confidence interval; HR – Hazard ratio for pleural infection; IMD – Index of multiple deprivation.

3.3.2. Factors associated with pleural infection

Factors associated with pleural infection are shown in Table 3-2. In the multivariable model, characteristics associated with an increased risk of pleural infection included male gender (HR 1.67, 95% CI 1.27-2.24, p<0.001), number of co-morbidities (HR 1.13, 95% CI 1.10-1.16, p<0.001) and having undergone pleural drainage (HR 1.61, 95% CI 1.28-2.02, p<0.001) or thoracic surgery (HR 2.23, 95% CI 1.64-3.02, p<0.001). Pleural infection was seen less frequently in patients diagnosed as outpatients (HR 0.12, 95% CI 0.02-0.86, p=0.035), patients with non-pleural mesothelioma (HR 0.81, 95% CI 0.67-0.97, p=0.025), patients who underwent thoracoscopy (HR 0.65, 95% CI 0.51-0.83, p<0.001), percutaneous biopsy (HR 0.76, 95% CI 0.62-0.94, p=0.009) or pleurodesis (HR 0.44, 95% CI 0.35-0.55, p<0.001), and patients who had received chemotherapy (HR 0.60, 95% CI 0.43-0.82, p=0.001). Pleural infection was associated with a higher number of pleural procedures (HR 1.51, 95% CI 1.41-1.61, p<0.001).

There was evidence of interaction between several variables relating to pleural infection (Appendix 3). However, sensitivity analyses controlling for the interacting variable did not alter the observed association any of the variables tested.

3.3.3. Survival

20,363 deaths occurred over 24,453 patient-years. Participants censored on 28/03/2016 had been followed up for a minimum of 14.9 months (range 14.9-134.5, median 39.6).

Overall median survival was 6.9 months (IQR 2.3-16.3), increasing to 7.8 months (IQR 2.6-17.1) in patients diagnosed after 2008 (n= 13,482). Median survival was 6.2 months in patients who experienced pleural infection (IQR 2.6-14.9) compared with 7.0 months (IQR 2.3-16.4) in those who did not (unadjusted HR 1.11, 95% CI 1.02-1.22, p=0.021). Kaplan Meier curves, separated by pleural infection, are shown in Figure 3.2.

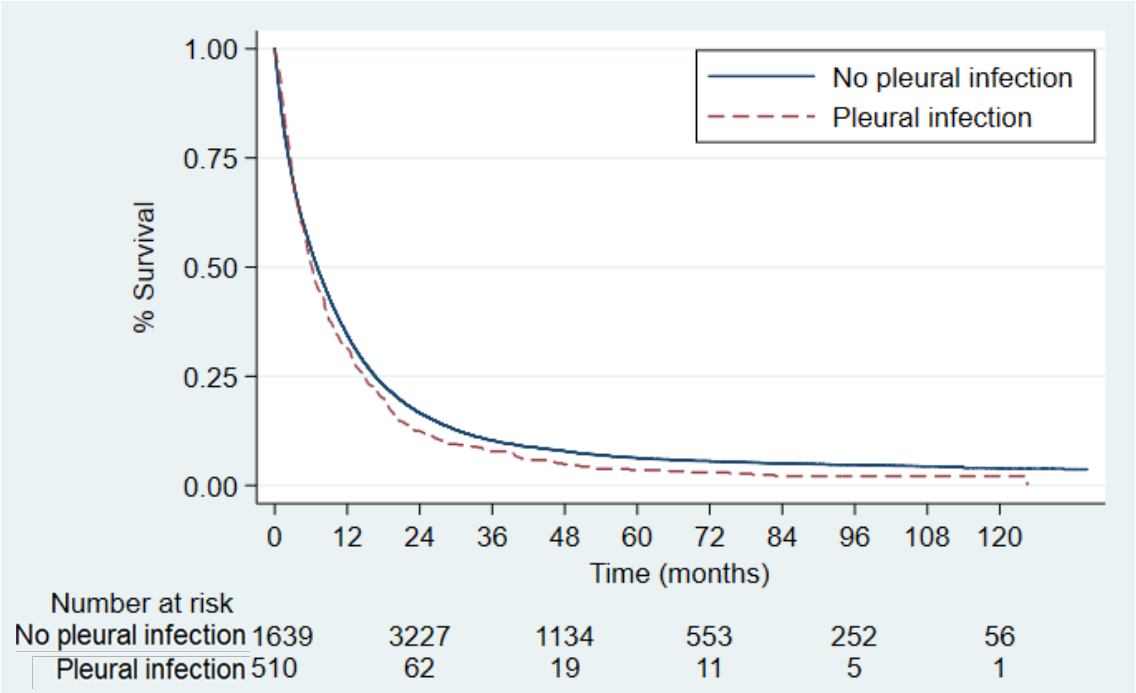


Table 3-2 Kaplan Meier curves demonstrating survival (unadjusted) in patients who did and did not experience pleural infection

3.3.4. Primary outcome

The risk of dying from any cause was higher after pleural infection, both in the immediate (30 day) post-infection period (adjusted HR 1.81, 95% CI 1.47-2.23, p<0.001) and in the longer term (30+ days) post-infection (adjusted HR 1.80, 95% CI 1.63-1.99, p<0.001). Full results of the unadjusted and adjusted survival models are shown in Table 3-3.

	Unadjusted analysis			Adjusted analysis		
	HR	95% CI	p	HR	95% CI	p
Pleural infection						
Pre-infection/no infection	1	-		1	-	-
First 30 days post-infection	1.72	1.40 to 2.12	<0.001	1.81	1.47 to 2.23	<0.001
30+ days post-infection	1.68	1.52 to 1.86	<0.001	1.80	1.63 to 1.99	<0.001
Male gender	1.24	1.20 to 1.29	<0.001	1.26	1.21 to 1.30	<0.001
Age at diagnosis ≤65	1	-	-	1	-	-
66-70	1.19	1.14 to 1.24	<0.001	1.17	1.12 to 1.22	<0.001
71-75	1.38	1.32 to 1.44	<0.001	1.34	1.28 to 1.39	<0.001
76-80	1.71	1.64 to 1.79	<0.001	1.59	1.53 to 1.67	<0.001
≥81	2.20	2.12 to 2.30	<0.001	1.99	1.90 to 2.08	<0.001
IMD quintile						
1 (least deprived)	0.94	0.90 to 0.98	0.004	0.95	0.91 to 0.99	0.013
2	0.93	0.89 to 0.97	0.001	0.95	0.91 to 0.99	0.018
3	1	-	-	1	-	-
4	0.98	0.94 to 1.02	0.327	0.98	0.93 to 1.02	0.298
5 (most deprived)	1.03	0.99 to 1.08	0.145	1.02	0.98 to 1.07	0.279
Missing	0.20	0.18 to 0.23	<0.001	0.27	0.23 to 0.31	<0.001
Rural/urban location						
Urban ≥10,000 population	1	-	-	1	-	-
Town and Fringe	1.05	1.01 to 1.10	0.025	1.03	0.98 to 1.08	0.253
Village	0.99	0.94 to 1.04	0.722	1.01	0.96 to 1.07	0.686
Hamlet/ isolated dwelling	0.92	0.85 to 0.99	0.049	0.96	0.88 to 1.04	0.268
Mode of initial attendance						
Outpatient appointment	1	-	-	1	-	-
Hospital inpatient	2.26	2.08 to 2.46	<0.001	1.16	1.06 to 1.28	<0.001
Operation/procedure	2.26	2.07 to 2.46	<0.001	1.06	0.97 to 1.17	0.215
Diagnosed after 2008	0.86	0.84 to 0.89	<0.001	0.87	0.85 to 0.90	<0.001
No. of comorbid codes	1.02	1.02 to 1.03	<0.001	0.99	0.98 to 0.99	<0.001
Non-pleural mesothelioma	1.06	1.03 to 1.09	<0.001	0.95	0.92 to 0.98	<0.001
Asbestos exposure	1.05	1.01 to 1.09	0.017	1.07	1.03 to 1.12	<0.001
Pleural plaques	1.20	1.13 to 1.27	<0.001	1.10	1.05 to 1.18	0.001
Pleural interventions						
Pleural drainage/aspiration	0.89	0.87 to 0.92	<0.001	1.21	1.16 to 1.26	<0.001
Thoracoscopy	0.65	0.63 to 0.67	<0.001	0.88	0.84 to 0.92	<0.001
Percutaneous pleural biopsy	0.93	0.90 to 0.96	<0.001	1.07	1.03 to 1.11	<0.001
Pleurodesis	0.65	0.63 to 0.67	<0.001	0.88	0.84 to 0.91	<0.001
Total no. of pleural procedures	0.87	0.86 to 0.87	<0.001	0.87	0.85 to 0.88	<0.001
Average no. of hospital episodes per year	0.97	0.96 to 0.97	<0.001	0.98	0.97 to 0.98	<0.001
Treatment received						
Chemotherapy	0.83	0.81 to 0.86	<0.001	0.96	0.93 to 0.99	0.031
Radiotherapy	0.64	0.55 to 0.74	<0.001	0.97	0.83 to 1.12	0.647
Thoracic surgery	0.90	0.88 to 0.93	<0.001	1.05	1.01 to 1.10	0.025

Table 3-3 Factors associated with all-cause mortality in 22,149 patients with mesothelioma, from adjusted and unadjusted survival models. All variables were included in the multivariable model.

Abbreviations: CI – confidence interval; HR – Hazard ratio for mortality; IMD – index of multiple deprivation

In the multivariable model, factors associated with increased all-cause mortality were age, male gender, being diagnosed as an inpatient, undergoing percutaneous biopsy, undergoing a drainage procedure, documented asbestos exposure or pleural plaques, and having undergone thoracic surgery. Non-pleural mesothelioma, being diagnosed after 2008, being less deprived, undergoing thoracoscopy or pleurodesis, fewer pleural procedures and receiving chemotherapy were all associated with reduced mortality.

3.3.5. Secondary analyses

18,587 (91.3%) deaths were due to mesothelioma. Mesothelioma-specific mortality outcomes were similar to those for all-cause mortality (Appendix 3). Additionally, the survival model did not change substantially when adjusted for confounders alone compared with confounders and mediators. Finally, sub-group analysis of pleural mesothelioma patients yielded comparable results to the main analysis (Appendix 3).

3.4. Summary of findings

This large, population-level cohort study contradicted the hypothesis that pleural infection was associated with longer survival in mesothelioma. The data showed that pleural infection was associated with higher mortality, both in the immediate post-infection period and in the longer-term.

The data available from HES were limited, however, and information on certain prognostic factors, e.g. patients' performance status and tumour histological type, was not available. This may have caused confounding to affect the observed result. Additionally, the microbiological organisms causing pleural infection were not recorded.

As previously stated, it is recognised that different bacterial species have widely differing physiological effects, and it was unfortunate that this could not be explored further with these data in regards to survival in mesothelioma. These limitations are discussed in greater length in Chapter 6.

The findings of this study must be interpreted within the limitations of an observational study. Causality cannot be determined and, if the association between pleural infection and increased mortality in mesothelioma is genuine, the direction of the relationship is not known. It may be that dying patients were more likely to develop pleural infection, rather than infection contributing to earlier death.

Chapter 4 – The TILT trial

Some of the work in this chapter has been published:

Bibby AC, Torgerson DJ, Leach S, Lewis-White H & Maskell NA. Commentary: considerations for using the 'Trials within Cohorts' design in a clinical trial of an investigational medicinal product. *Trials*. 2018;19(1):18.

4.1. Background

4.1.1. Intra-pleural immunotherapy in mesothelioma

As discussed in Chapter 1, the treatment options for MPM are limited. The disease is currently incurable, with median survival less than 1 year from diagnosis.(1, 30, 36, 38, 188) Pemetrexed and cisplatin combination chemotherapy extended survival by 2.8 months compared with single-agent cisplatin, however chemotherapy is not suitable for everyone.(2, 4, 38). The addition of bevacizumab, a targeted antagonist of vascular endothelial growth factor (VEGF), to chemotherapy conferred a further 3 months survival benefit compared with placebo.(6) Unfortunately, access to bevacizumab is limited, as it is not yet licensed for use in MPM in the UK or the US.

New therapeutic options are urgently required for MPM, and immunotherapy is an appealing choice. MPM is an immune-evasive tumour that is able to suppress protective populations of CD8+ effector T cells and antigen presenting cells (APC) in the pleura, whilst also upregulating CD25+ regulatory T cells (Tregs).(11, 12, 67-69). The ability to overcome this local immunosuppression and maintain normal immune cell responses in the pleura has been shown to be associated with longer survival.(13, 69, 70, 189).

Some of the immunosuppression associated with MPM occurs as a result of exploitation of the immune checkpoint pathway. Approximately 40% of MPM tumours express the programmed death 1 ligand (PD-L1) and, consequently, are able to down-regulate effector T cell activity and inactivate protective anti-tumour immune responses.(190, 191) The use of immune checkpoint inhibitors (ICI) to interrupt the interaction between the programmed death 1 (PD-1) receptor and PD-L1, and preserve anti-cancer immune activity has been investigated in MPM.(15, 17, 49, 50, 192). However, to date, there is no published RCT evidence supporting the efficacy of ICI to extend survival with MPM, although several negative trials have been published.(51, 75) Recently, the combination of ipilimumab and nivolumab as a first-line therapy was associated with longer overall survival in comparison to standard chemotherapy, but the full trial report has yet to be published.(80)

Like most pharmaceutical agents, ICI and chemotherapy carry a risk of toxicity, which can have serious consequences.(4, 17) Many patients with MPM are reluctant to receive systemic anticancer treatment due to concern about side effects and reluctance to compromise their QoL.(48) A treatment approach that could reduce the risk of side effects would be welcomed by this patient population.

Topical administration of therapeutic agents is one potential way of reducing side effects. In MPM, indwelling pleural catheters (IPC) present an opportunity to deliver medications directly into the pleural cavity. This could maximise the concentration of the drug in the immediate tumour environment and may limit systemic absorption, leading to fewer side effects.(18, 19) It is not known whether ICI can be administered

safely via an IPC, but alternative immunotherapy agents, i.e. bacterial products, have been administered intra-pleurally for several decades, with few complications. As shown by the systematic review, summarised in Chapter 2, it is unclear from the current literature whether bacterial products have any effect on survival in people with pleural malignancy, whether due to MPM or other malignancies.(176)

Clinical equipoise exists, therefore, as to whether bacterial products could be re-purposed for use as anti-cancer agents in MPM. It is an area of interest for clinicians, patients and mesothelioma stakeholders, and was highlighted as such by the James Lind Alliance in a 2015 priority setting partnership exercise.(162) The question "Is there a role for intrapleural immunostimulants (a drug designed to stimulate an anti-cancer immune response, such as corynebacterium parvum extract)?" was designated the eighth most important question in mesothelioma research.

The Trial of Intrapleural bacteriaL immunoTherapy (TILT) was designed to address this question, focussing on two bacterial products: OK432 and BCG. These bacterial products were chosen based on *in vitro* and *in vivo* evidence demonstrating pro-inflammatory activity and associated cytotoxic effects.(98, 100, 110, 114) As described in Chapter 1, it was felt that the trial within a cohort (TwiC) methodology would be well suited to undertaking this trial in the MPM population. Since the TwiC design had not been used in patients with MPM previously, a feasibility trial was planned.

4.1.2. The TwiC design

The TwiC design (also known as the cohort multiple randomised controlled trial or cmRCT methodology) is a highly pragmatic approach to randomised clinical trials.(136) Patients who are already participating in a longitudinal, observational cohort study are screened to determine whether they are eligible to participate in the trial. Eligible participants are selected at random to be offered the trial intervention, with non-selected eligible participants acting as controls from within the cohort (Figure 4.1). A key tenet of the TwiC design is that after randomisation takes place, people selected to be offered the trial intervention are told about the trial, provided with information about the intervention and asked to consent to receive it (i.e. the intervention arm is open label), whilst control patients in the cohort are not informed about the trial or the intervention and are not required to give any additional consent (i.e. they are blinded).

The TwiC design has several potential benefits, including efficient recruitment, reduced cross-over between arms and lower risk of attrition from the control group. Additionally, there is potential to undertake multiple trials within the same cohort, thus enhancing efficiency and reducing some of the delays and costs associated with setting up and recruiting to clinical trials.(136, 157, 193) TwiCs also replicate real-life clinical care more faithfully than standard RCTs. In clinical practice, patients are told about interventions if and when they are going to receive them, and not if they are not. The exact same practice occurs in a TwiC. In contrast, in a standard RCT, all patients are informed about the intervention, despite the fact that approximately half will never receive it. Furthermore, in a blinded RCT, participants may never know whether they received the intervention or not.

TwiCs are highly pragmatic, therefore, and can provide useful information on the effectiveness of interventions.(136, 149, 157) The counterpoint to this is that TwiCs are less suited to explanatory studies or early phase trials where safety and efficacy are being assessed. These types of trials tend to require strict protocols, with most variables tightly controlled, so that the true effect of the intervention can be evaluated under perfectly regulated conditions.(149) Because the safety profile of intra-pleural bacterial products was well established and their biological effect had been demonstrated *in vitro* and *in vivo*, a pragmatic methodology was preferred for this research. Additionally, if patients were unwilling to take chemotherapy due to concern about side effects, they may make the same decision about intrapleural bacterial immunotherapy. In such a scenario, a pragmatic, effectiveness study would provide a better evaluation of the potential impact of this treatment in the real-world MPM setting. Finally, given the current dearth of effective treatment options for MPM and the recruitment challenges that have faced historic clinical trials in MPM, the potential efficiency associated with recruiting from within an existing cohort was appealing.

4.1.2.1. Designing a CTIMP TwiC

Since its initial description in 2010, the TwiC design has been used around the globe, in areas as diverse as public health, oncology, rheumatology and complimentary medicine.(194-199) However, at the time TILT was designed, the methodology had never been applied to a clinical trial of an investigational medicinal product (CTIMP). For safety reasons, CTIMPs are subject to more stringent regulations and governance than other research trials.(200-205)

In order for TILT, or indeed any CTIMP using the TwiC design, to comply with these regulations, certain methodological considerations had to be appraised during the design phase of TILT.(206) Ultimately, it was necessary to make certain specifications within the trial protocol, clarifying the distinction between cohort participation and trial participation (see Section 4.1.2.4.).

4.1.2.2. Trials suitable for the TwiC design

The TwiC methodology is highly pragmatic and can provide valuable information about the real-life utility and effectiveness of interventions. The design is less suitable for explanatory trials aiming to evaluate whether an intervention has an effect under ideal (and therefore tightly controlled) conditions, particularly early-phase clinical trials.(136) In the context of CTIMPs, therefore, the TwiC approach is more appropriate for trials in the later phases of clinical evaluation.

Specific factors that make the TwiC design unsuitable for early-phase clinical trials include the necessary use of standard care as the comparator arm. Not only are placebo-controlled trials not possible, but trials that entail additional interventions or investigations in the control arm, outside the remit of usual care, are also incompatible with the TwiC design. This is because the additional procedures would be considered research activities and control participants should provide consent to undergo such activities. However, the blinding of control participants is an inherent element of the TwiC design and obtaining additional consent from controls for trial-specific procedures would undermine this. In contrast, participants who receive the intervention in a TwiC

do so in an open-label fashion. This enables a "patient-centred" consent process in which every participant is informed about, and gives consent for, the precise activities and interventions that they will undergo. However, in combination, these factors make the TwiCs design unsuitable for early-phase CTIMPs, evaluating drug safety and efficacy.

4.1.2.3. Clinical trials regulations

Clinical research involving pharmaceutical products is guided by the International Committee for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Statement on Good Clinical Practice (GCP).(202) This document provides an international standard for ethical and scientific quality in research involving human participants, based on the principles set out in the Declaration of Helsinki. In the European Union (EU), this guidance has been transcribed into law in the form of European Directive 2001/20/EC, also known as the EU Clinical Trials Directive. Similar legislation has been produced by the Food & Drug Administration (FDA) in the US,(203) and other regulatory authorities in other countries. It is a legal requirement that all CTIMPs conducted in these countries adhere to the relevant regulations.

The primary purpose of clinical trials legislation is to protect the safety, well-being and rights of trial participants. A fundamental component of this is informed consent, whereby research participants are given information about all research procedures, including any potential risks associated with those activities. Only once they have had time to consider this information will the participant be in a position to make an autonomous, informed decision regarding participation in the research.

In randomised trials with participants who have capacity, the process of randomisation is a research activity and should only occur once the participant has consented to take part in the trial. Although both pre-randomisation and randomisation without consent designs have been used historically, notably as part of the Zelen design, they were generally considered unethical, with significant potential to damage the doctor-participant relationship.(137, 138, 143)

Initially concerns were voiced that the TwiC design entailed pre-randomisation, however, proposal of a 'staged consent' model resolved this issue.(142, 146) With the staged consent process, all cohort participants provided initial consent at the time of enrolling, which included specific agreement to:

- allow their cohort data to be used to screen their eligibility for clinical trials;
- undergo random selection for future trials for which they were eligible; and
- permit use of their data as comparison data for clinical trials, even in the event of non-selection for that trial.

With all participants having consented to the above points, people randomly allocated to the trial intervention arm were asked to provide second consent, essentially agreeing to receive the trial intervention.(146) Control patients were not required to provide any additional consent as they were not subject to any additional research processes. Thus, all participants provided consent for every research activity they experienced.

4.1.2.4. Separating cohort and trial activities

Applying the staged consent process to TILT enabled explicit separation of research processes into either cohort-related or trial-related activities. Based on the model described above, screening for TwiCs, random selection and provision of control data were designated cohort activities, covered by the cohort consent form. IMP administration was a trial activity, covered by the trial consent form. Using this approach, trial participants were specified as those who had signed the trial consent form, whilst everyone else, including control patients, were participating in the cohort only (albeit a comparative cohort with randomisation element).

This approach was essential to maintain legality in applying the TwiC methodology to a CTIMP. According to article 4.8.10(c) of ICH GCP, participants in trials involving investigational medicinal products (IMP) must be informed about the IMP and the probability of being assigned to it.(202) Without staged consent, TwiCs fail to meet this requirement, as control participants are neither informed about the IMP nor the probability of being selected to receive it. However, by specifying that control patients are cohort participants only, and that the trial population consists exclusively of participants who have signed the second consent form (i.e people who were selected to receive the intervention and agreed), adherence to ICH GCP requirements was ensured.

This approach removed ambiguity, ensured legality and is likely to have facilitated the Medicines and Healthcare Products Regulatory Agency (MHRA) and Health Research Authority (HRA) approval processes. However, it created complexity in other areas of trial design and management, which are pertinent if future CTIMP TwiCs are planned.

4.1.2.5. Costings

Separating research activities into cohort-related or trial-related required careful allocation of costs to ensure that funders were satisfied with how grant monies were utilised. For TILT, even though control participants were not, strictly speaking, participating in the trial, the intensity of their follow-up was increased to match the trial assessment schedule. Since this data was crucial to the analysis of trial outcomes, it seemed appropriate to include the costs in the funding application for the trial, with a clear explanation that they would cover the cost of controls in the cohort. Future CTIMP TwiCs will need to have adequate funding in place to cover both the research costs of trial participants and any additional processes for controls in the cohort.

Another UK-specific financial consideration related to study support resources from the National Institute for Health Research (NIHR) Clinical Research Network (CRN). Commensurate with the complexity of the research, a higher level of support is available for randomised trials than for observational studies. By designating controls as cohort participants rather than trial participants, we limited the level of study support that participating NHS hospitals could receive for these participants. This factor was highlighted when approaching centres to participate in the trial and was not considered problematic. However, if a full-scale trial is planned, the financial impact will be greater and may reduce some sites' enthusiasm to participate.

4.1.2.6. Study assessment schedule

CTIMP schedules tend to consist of more frequent data collection visits than most observational studies.(149) However, to obtain meaningful comparison data in a TwiC, follow-up of cohort-based controls needs to match the trial assessment schedule. Since it would be impossible to design a cohort with a visit schedule that matched all potential future TwiCs, the protocol for the cohort study in which TILT was embedded (called ASSESS-meso) was designed with a flexible follow up regimen that could be altered based on clinical or research requirements. Thus, the assessment schedule of cohort participants could be adapted if they were identified as TwiC controls without violating the cohort protocol, without subjecting participants to extra assessment visits that may be considered 'trial-related', and without requiring further consent.

Even with flexible cohort follow up, if the trial assessment schedule was too demanding, there was a risk that altering controls' follow-up to match it may induce curiosity or anxiety, leading to inadvertent or explicit unblinding of controls. In addition, it could be considered unethical to place excessive research demands on the control population, particularly for MPM patients who had incurable cancer and a limited lifespan. For this reason, the TILT assessment schedule was designed to be as undemanding as possible, whilst remaining safe and sufficient to generate relevant outcome data.

4.2. Methods

4.2.1. The cohort - ASSESS-meso

4.2.1.1. Study design & aim

ASSESS-meso was a prospective, multicentre, pragmatic cohort study of patients with mesothelioma. The aim was to collect longitudinal data on the natural history of mesothelioma, to identify different phenotypic sub-groups of the disease and to provide a resource for future TwiCs.

Specific objectives included the collection of longitudinal data across multiple domains including clinical, biochemical, biometric and psychological parameters. The collection and analysis of biological samples, including blood and pleural fluid, was intended to allow investigation of potential biomarkers and exploration of clinical and biochemical factors that influence outcome. Finally, longitudinal data collected in the cohort provided control group data for TwiCs conducted within the cohort.

4.2.1.2. Study design

ASSESS-meso was a prospective, observational cohort study with a pragmatic and flexible assessment schedule.

4.2.1.3. Participants

To be eligible to participate in ASSESS-meso, patients were required to meet all of the following criteria:

1. Histological, cytological or clinico-pathological diagnosis of MPM, confirmed at multidisciplinary team (MDT) meeting.

2. Willing and able to comply with study follow up assessments.
3. Has capacity, as defined by the 2005 Mental Capacity Act.

Additionally, to be eligible, none of the following criteria could apply:

1. Aged less than18 years old.
2. Unable to give written informed consent.
3. Declined ongoing hospital follow up.

4.2.1.4. Setting

ASSESS-meso was initially set up in two tertiary referral pleural centres in the UK (Southmead Hospital, Bristol and the Churchill Hospital, Oxford). After six months an additional hospital was set up as a study centre (Musgrove Park Hospital, Taunton), and thereafter five further sites were opened to recruitment (Hywel Dda Health Board, West Wales; Royal United Hospital, Bath; Derriford Hospital, Plymouth; Leicester Royal Infirmary; Manchester University Foundation Trust).

4.2.1.5. Recruitment and consent

Potential participants were identified at local mesothelioma and lung cancer MDT meetings. Patients who met the eligibility criteria were approached by a member of the research team at their subsequent clinic appointment and invited to discuss the study with a member of the research team. Potential participants were provided with the study participant information sheet (PIS) and given sufficient time to read it.

Patients were given the opportunity to ask questions before being invited to give written, informed consent to take part in the study. Participants who wished to have longer to consider the study or who were unable to enrol in the study at their initial appointment were offered the opportunity to return at a later date. There was no formal time limit between receiving a diagnosis of MPM and enrolling in the cohort, although it was recommended that enrolment occurred within six weeks of diagnosis to prevent survivorship bias.

The ASSESS-meso consent form included a section relating to TwiCs. Participants were asked to provide consent to be screened for future trials, to be randomly selected to join those trials and to provide comparative data for those trials even if not selected to join them. Participants who did not want to be considered for future trials were welcome to enrol in ASSESS-meso but were not eligible to be screened for TwiCs.

4.2.1.6. Study assessments

Participants were followed up from enrolment until death or withdrawal from the study. Baseline assessment was completed at enrolment, with follow up assessments undertaken when participants attended appointments as part of standard clinical care, with a minimum frequency of 3 monthly. More frequent follow up assessment was permitted if indicated for clinical reasons or if participants were providing data for a TwiC.

At each study assessment, data was collected relating to clinical status, radiological imaging, blood tests and patient-reported outcome measures (PROMs). Baseline clinical

data included information on patient co-morbidities and current medications, asbestos exposure history, diagnostic investigations and tumour characteristics. If a pleural effusion was present, an intervention history was obtained. Follow up clinical data focussed on treatment received, interactions with healthcare service, changes to medications and additional interventions that had occurred since the previous visit.

Radiological assessment at baseline included chest radiography (CXR), thoracic ultrasound (TUS) and computed tomography scan (CT) of the thorax, performed within 4 weeks of enrolment. Tumour stage, based on the International Association for the Study of Lung Cancer (IASLC) eighth edition,(207) was recorded, as were the presence of pleural plaques, non-expandable lung (NEL) or other thoracic abnormality. Follow up radiological imaging was undertaken at the discretion of the clinician, with the anticipation that most participants would have a CT scan every 6 months. Follow up CT scans were assessed for tumour stage and radiological response, evaluated based on the modified response evaluation criteria in solid tumours (mRECIST).(208)

Baseline blood tests included full blood count (FBC), urea and electrolytes (U&E), liver function tests (LFT), C reactive protein (CRP), lactate dehydrogenase (LDH), total protein, random glucose and serum mesothelin. Blood tests taken at follow up visits included FBC, U&E, LFT, CRP and mesothelin.

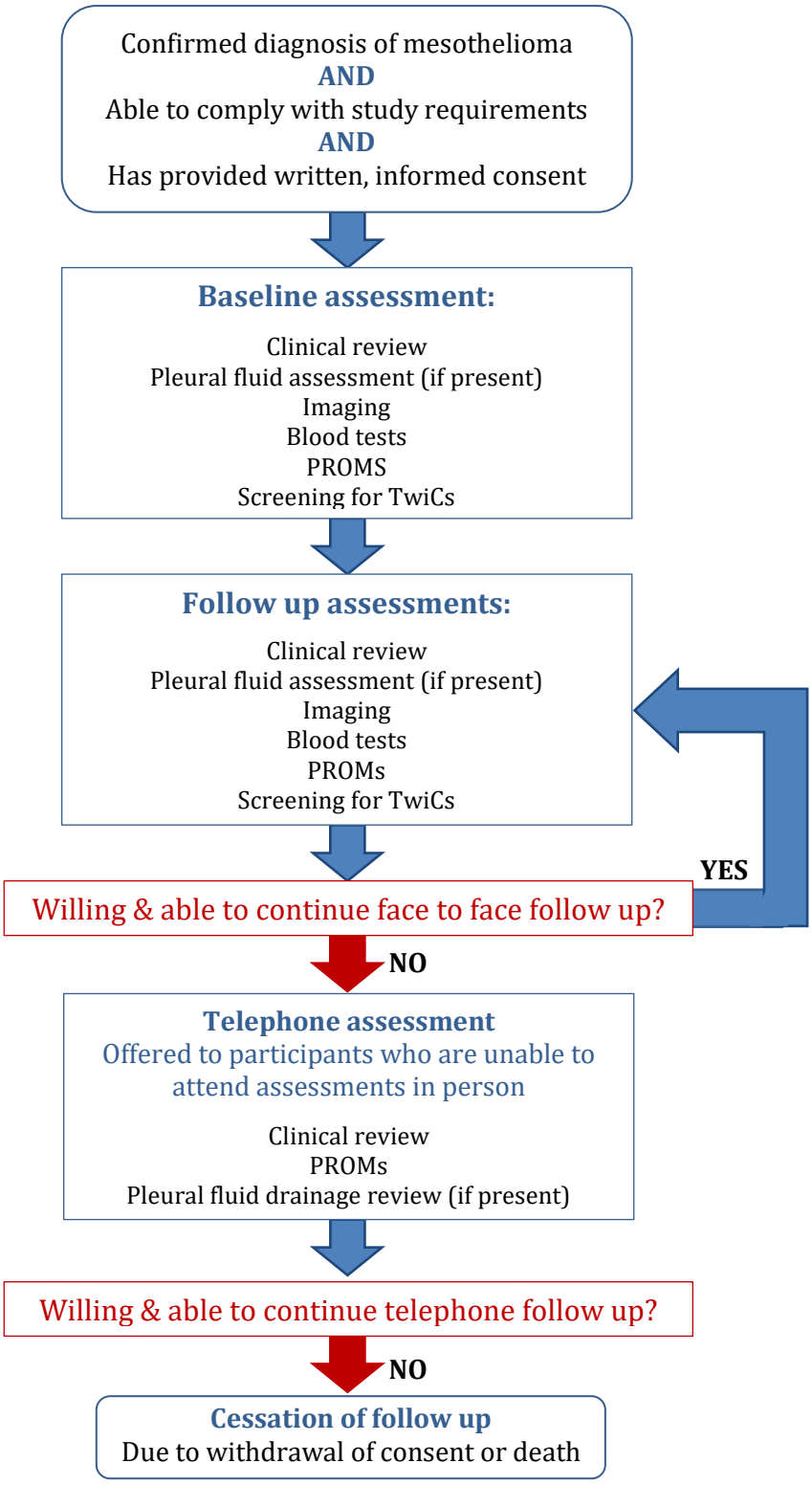


Figure 4.1 ASSESS-meso study schema

At every assessment, participants were invited to complete a set of PROMs, which included 10cms visual analogue scales (VAS) for breathlessness, chest pain and sweating and a brief QoL questionnaire (EuroQol 5D health questionnaire, EQ-5D-5L). At each assessment, cohort participants were screened for eligibility to participate in TILT.

Participants who were unable to attend regular study follow up appointments, either as a result of frailty or geographical distance from a study centre, were offered telephone follow up. Assessments included a brief clinical review with PROMs sent for completion via post or email. For participants undergoing telephone follow up, the most recent blood test and imaging data were imported from other centres, where available. Figure 4.1 Shows the study schema. Copies of the study case report forms (CRF) are provided in Appendix 4.

4.2.1.7. Study registration and regulatory approvals

ASSESS-meso was registered on ISRCTN (61861764). Research Ethics Committee Approval was obtained on 03/02/2017 (ref 17/SW/0019) and Health Research Authority approval on 16/2/2017 (IRAS ID 220360).

4.2.2. The trial – TILT

4.2.2.1. Trial design & aim

TILT was a multicentre, single-blind, three-arm, randomised feasibility trial of intra-pleural OK432 *vs* intra-pleural BCG *vs* usual care in people with MPM, based on the TwiC methodology.

The aim of TILT was to assess the feasibility and acceptability of a full-scale trial using the same design. Specifically, the feasibility and acceptability of the TwiC methodology was explored. The study aimed to answer the question "Is it feasible to undertake a TwiC of intra-pleural OK432 and BCG in MPM and is it acceptable to participants and relatives?"

If feasibility was demonstrated, the intention was to progress to a full-scale TwiC of intra-pleural OK432 and/or BCG in MPM. The results of TILT would inform the design of the subsequent full-scale trial.

4.2.2.2. Participants

To participate in TILT patients were required to meet all of the following inclusion criteria:

- Histological or cytological diagnosis of MPM.
- Enrolled in ASSESS-meso, with consent to be randomly selected for future trials.
- IPC in situ that has drained more than 50ml of fluid on previous 3 drainages.

  OR has a pleural effusion suitable for IPC insertion and willing and able to undergo IPC insertion.
- No chemotherapy in preceding 4 weeks and none planned for trial period or within 4 weeks of trial completion.
- Performance status (PS) ≤2, or 3 and felt clinically suitable for trial.
- Predicted survival ≥12 weeks from enrolment.
- Able to give written informed consent & willing to meet trial requirements.

Additionally, to be eligible, participants must have none of the following exclusion criteria:

- No IPC in situ with a contra-indication to IPC insertion.
- Clinico-radiological diagnosis of MPM.
- Trapped lung with <50% pleural apposition on x-ray.
- Moderately heavy or heavily loculated pleural effusion.
- Known immunodeficiency or immuno-suppressive medication.
- Intercurrent infection (pleural or elsewhere) or clinical signs of sepsis.
- Known sensitivity or allergy to OK432, BCG or penicillin.
- Previous treatment with immunotherapy.
- Currently enrolled in any other interventional clinical trial.
- Brain metastases or central nervous system involvement of MPM.
- Pregnancy or lactation, current or planned during the study period.
- Age <18.

4.2.2.3. Setting

The trial took place at three hospital sites in the South of England: Southmead Hospital, Bristol; the Churchill Hospital, Oxford; and Musgrove Park Hospital, Taunton.

4.2.2.4. Interventions

Participants were randomly allocated to receive either:

- Intra-pleural OK432;
- Intra-pleural BCG or;
- Usual care with continued follow up in ASSESS-meso.

OK432 is a heat-treated, penicillin-killed, freeze-dried streptococcal preparation derived from *Streptococcus pyogenes* group A2 (Picibanil, Chugai Pharmaceutical Ltd, Tokyo, Japan). It is composed of dried streptococcal cells containing penicillin G potassium at a dose of 26,900 units/mg of dried cocci. A dose of 1 Klinische Einheit (KE) is equivalent to 0.1 mg of dried streptococci. OK432 was supplied as a dry white powder in vials of 5KE. For the trial, OK432 was reconstituted in 50ml of sterile 0.9% saline immediately prior to instillation into the pleural cavity. The original dose of OK432 in TILT was 10 KE. However, after the first three participants had been enrolled to the trial an urgent safety measure (USM) was passed advising a reduced dose of 5KE be used in participants who were older, had poorer performance status or a greater number of co-morbidities.

BCG is a live attenuated, low-virulence strain of *Mycobacterium bovis* prepared from a culture of Bacillus Calmette-Guérin (OncoTice, Merck Sharp & Dohme Ltd, The Netherlands). It comprises a freeze-dried preparation of bacilli, with each 12.5mg vial containing 2-8 x 10^8 colony forming units (CFU). BCG was supplied as a dry powder, which was reconstituted in 50ml of sterile 0.9% saline prior to administration. The initial trial dose of BCG was 0.4-1.6 x 10^7 CFU (1ml of reconstituted solution), however, after the USM was passed, a reduced dose of 0.2-0.8 x 10^7 CFU (0.5ml of reconstituted solution) was advised for patients at high risk of adverse events or who would find it

difficult to manage an adverse event. For example, elderly patients, patients with performance status of 2-3, patients with multiple medical co-morbidities, especially cardiac or renal, and patients who lived alone or had high care needs.

The IMP was delivered as a single dose, via an indwelling pleural catheter, within 14 days of randomisation. For the intervention visit, participants attended hospital and underwent medical assessment to ensure they remained suitable to receive the IMP. Effusions were drained to dryness to ensure IPC patency and a CXR was performed to exclude NEL. If patients remained eligible, 3mg/kg of 1% lignocaine (to a maximum of 250mg) was instilled via the IPC, followed by the IMP and a flush of 20mls of normal saline. The IPC was disconnected and the IMP left within the pleural cavity for 1 hour. After 1 hour, the IPC was drained. The participant was observed in hospital for another hour before returning home.

4.2.2.5. Outcomes

The primary outcome was feasibility. The study was determined to be feasible if the following criteria were met:

- Recruitment rate of ≥66% to time and target.
- Attrition rate of <10% after randomisation, where attrition was defined as participants who declined to receive an IMP if randomised to receive it or who declined or failed to complete follow up in the cohort if allocated to control.
- Data completeness rates >90%.

Certain features of the TwiC design were evaluated for feasibility. Specifically, data were collected on:

- The proportion of participants offered OK432 or BCG who declined to receive it.
- The number of participants in the control arm who were unblinded.
- The characteristics and outcomes of people who consented to join the cohort but declined to be considered for future trials.
- The acceptability of TILT to participants and family members, evaluated during qualitative interviews after completion of the trial.

Secondary outcomes included adverse events, exploratory efficacy data and PROMs.

Adverse event (AE) data were collected at each assessment visit and evaluated for severity, expectedness and relationship to IMP. Severity was graded according to the Common Terminology Criteria for Adverse Events v5.0, whereby:

- Grade 1 was mild, causing no symptoms or mild symptoms, with no intervention required,
- Grade 2 was moderate, causing some limitation to activities of daily living, requiring minimal, local or non-invasive intervention,
- Grade 3 was severe or medically significant but not immediately life-threatening, causing disabling symptoms that limit self-care, requiring hospitalisation or prolongation of hospitalisation indicated,
- Grade 4 was life-threatening requiring urgent intervention, and
- Grade 5 was death related to AE.

Serious adverse events (SAEs), defined as any untoward medical occurrence that resulted in death, real and immediate threat to life, hospitalisation, prolongation of hospital stay, persistent or significant disability or incapacity or other health event which in the opinion of the clinician was serious (i.e. grade 3 or higher) were reported to the Sponsor within 24 hours. Adverse event data was reviewed by the Data Monitoring Committee (DMC) who had the capacity to close the trial early if significant safety concerns arose.

Expected AE were stated a priori and included death, admission to hospital or prolongation of inpatient hospital stay admission for a condition related to the underlying malignancy. Relationship to IMP was determined based on the temporal relationship between the AE and IMP administration, the likelihood of the AE being due to an alternative cause and the established effects and side effects of the IMP.

Exploratory efficacy measurements included survival, radiological tumour response rates, serial mesothelin values, pleural fluid drainage volumes and pleurodesis rates. Survival was calculated as date of diagnosis with MPM to date of death, as recorded on the death certificate. Surviving participants were censored on 02/06/2020. Radiological response rates were assessed by an independent thoracic radiologist who was blinded to trial allocation. To evaluate radiological response, tumour thickness was measured perpendicular to the chest wall or mediastinum at two positions on three different transverse CT slices, with responses defined according to the mRECIST criteria, whereby:

- complete response (CR) was disappearance of all target lesions with no evidence of disease elsewhere,
- partial response (PR) was a reduction in total tumour measurement of at least 30% from baseline,
- progressive disease (PD) was an increase in tumour thickness of 20% or more, and
- stable disease (SD) was as any change in tumour size that did not meet the above criteria.(208)

Serum mesothelin levels were measured at each study visit using ChemiLuminescent Enzyme Immunoassay technology (Lumipulse G; Fujirebio, Belgium). Pleural fluid drainage volumes were recorded at the time of drainage by community nursing staff who were not involved in the trial and were unaware of the patients' participation status. Pleurodesis was defined as "pleural fluid drainage volumes of less than 50mls on 3 consecutive drainages, with no significant residual fluid on thoracic imaging, or removal of IPC due to cessation of drainage with no further requirement for pleural intervention, whichever was recorded first".

Breathlessness, chest pain and sweats were completed by the patients at each visit using a 10cms VAS. QoL was evaluated using the EQ-5D-5L questionnaire, completed by participants at every study visit.

4.2.2.6. Sample size

In line with NIHR guidance on feasibility trials, the aim of the TILT trial was not to evaluate the clinical effectiveness of intra-pleural immunotherapy, but rather to assess whether a full-scale trial would be possible. According to that document, for feasibility trials "the sample size should be adequate to estimate the critical [feasibility] parameters to the necessary degree of precision."(209)

It was decided that the "critical feasibility parameter" for TILT was post-randomisation attrition, as this was the element of the TwiC design that was previously untested in this population. Specifically, it was felt that attrition rates of 20% or greater would render a full-scale trial unfeasible. For this reason, a target attrition rate of 10% with 95% CI of ±10% was used in the sample size calculation.

The following calculation was used to determine sample size:

$$95\%\ \mathrm{CI} = 1.96\ \times \sqrt{\frac{p\ \times\ (1-p)}{n}}$$

Where p was the predicted attrition rate and n was the sample size. The initial target sample size was 45 participants, which was sufficient to detect a 10% attrition rate with 95% CI of ±9%.

The target sample size was reduced before the study began, due to delays in obtaining OK432. The revised sample size was 30 participants, which would have detected a 10% attrition rate with 95% CI of ±11%, which was deemed acceptable.

A further reduction to the target sample size occurred 18 months into the trial. This was in response to slower than anticipated recruitment but (at that point) zero attrition. The new estimated attrition rate was 5%, which could be detected with a sample size of 12 people with 95% CI of ±12%.

4.2.2.7. Randomisation

Potential participants were screened for eligibility for TILT by a member of the trial team at every ASSESS-meso study visit, including initial enrolment. Randomisation occurred at the first visit that they met the TILT eligibility criteria (designated Day 0 of TILT). Participants were blinded to randomisation occurring, in line with the TwiC methodology, having already consented to randomisation at ASSESS-meso enrolment.

Randomisation was undertaken by a member of the trial team, using a centralised, concealed randomisation module embedded within the online study database. Randomisation occurred on a 1:1:1 basis, using a permuted block randomisation sequence, with blocks of varying and random sizes. Randomisation was minimised by performance status (assessed on the day of randomisation, after drainage of fluid and graded as 0 or ≥1) and tumour sub-type (classified as epithelioid/cytological diagnosis *versus* non-epithelioid). The randomisation sequence was generated by an independent database administrator using STATA (StataCorp LP) version 15 and was not visible to the trial team.

The clinical trial team were unblinded to the outcome of randomisation. Participants randomised to receive an IMP were informed of their allocation and provided with a PIS

about the trial. Participants allocated to control remained blinded to both the fact of randomisation and the outcome, and continued follow up in ASSESS-meso.

4.2.2.8. Schedule of assessments

The date of randomisation was designated Day 0. Participants allocated to OK423 or BCG were provided with the PIS and given up to 5 days to consider it. If they agreed to receive the IMP, they were scheduled in for an intervention visit within 14 days of randomisation. Control participants were not required to attend for an intervention visit. All participants underwent three subsequent trial assessment visits at week 3, week 6 and week 12. The TILT trial schema is shown in Figure 4.2.

Having completed the 12-week trial period, participants returned to follow up under the ASSESS-meso schedule. Data collection for ASSESS-meso continued until death, loss to follow up or withdrawal from ASSESS-meso.

1.1.1.1. Statistical methods

Descriptive statistics were used to summarise recruitment, attrition and data completeness rates. Participant characteristics were tabulated according to allocation at randomisation, i.e. intention to treat (ITT).

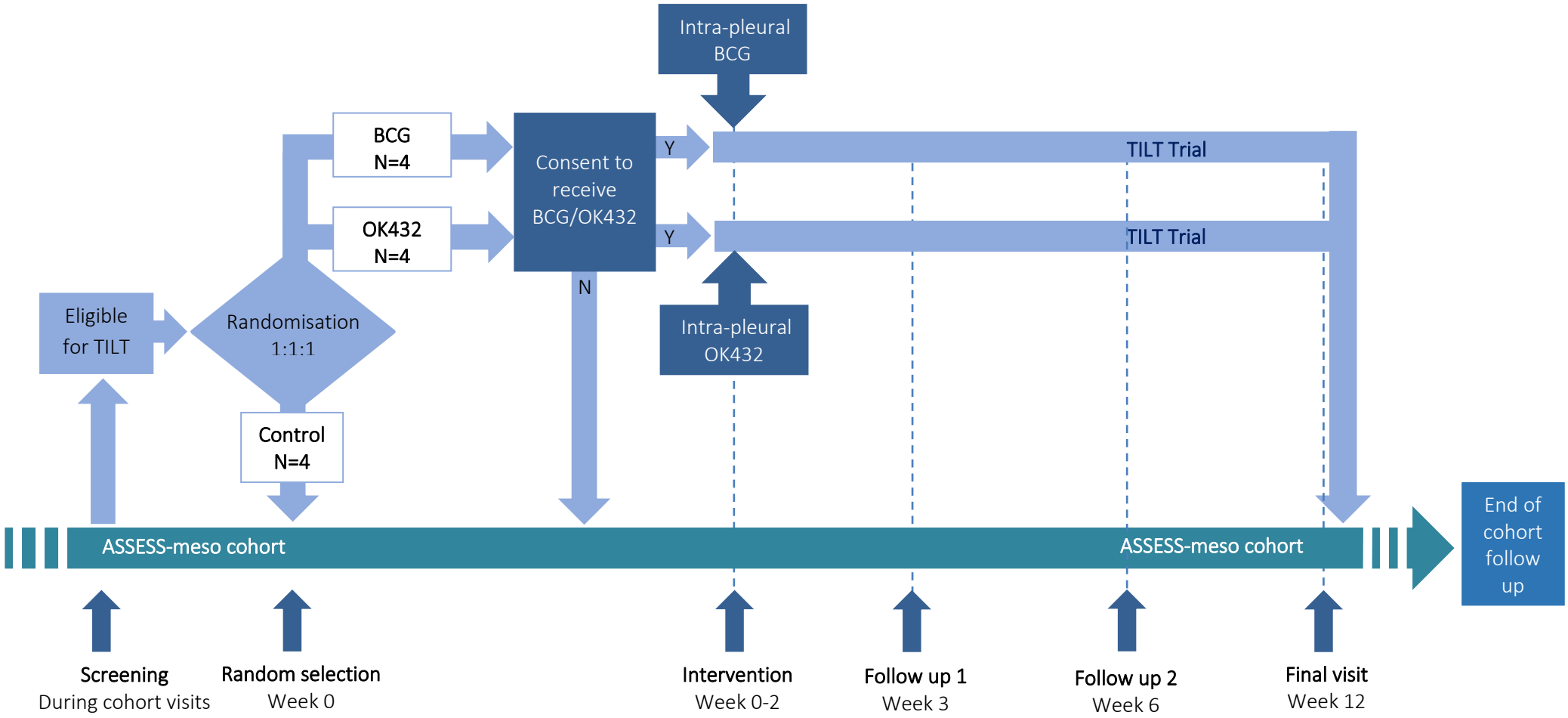


Figure 4.2 TILT trial schema

Secondary outcomes were summarised for each arm, based on allocation at randomisation. Because of the small number of participants, people randomised to receive either OK432 or BCG were combined to form one IMP group. Survival data were analysed using the Kaplan-Meier method, with unadjusted and adjusted Cox proportional hazards modelling. Survival rates were compared with national survival data and survival rates from previous MPM clinical trials. Pleurodesis rates and radiological response rates were compared between groups using Fisher's Exact test. Outcomes with repeat measurements, e.g. PROMS and blood tests, were analysed at each trial visit using two-way analysis of variance (ANOVA) modelling with multiple regression, based on ITT allocation.

Statistical analysis was undertaken using Stata (StataCorp LP) version 15.

1.1.1.2. Trial registration and approvals

The trial was registered on the European Clinical Trials Registry (EudraCT number 2016-004727-23) and the ISRCTN Register (10432197). Research Ethic Committee approval was granted on 02/05/2017 (ref 17/SW/0080), MHRA approval on 07/06/2017 (18524/0228/001-0002) and HRA approval on 19/06/2017 (IRAS ID 215394).

1.1.2. Challenges during trial set-up

4.2.3.1. Procurement of OK432

OK423 has been used as an intra-pleural pleurodesis agent in South East Asia for three decades. However, it does not have Marketing Authorisation (MA) from the European Medicines Agency (EMA) for use in the UK. The MHRA granted Clinical Trials

Authorisation (CTA) for OK432 to be used in TILT. This authorisation covered the storage and administration of OK432 at trial sites.

However, to legally import an unlicensed drug into the UK (or indeed the EU), a declaration is required from a Qualified Person (QP), stating the drug has been manufactured to the standards set out in Good Manufacturing Practice (GMP). The QP is also required to provide a batch release certificate, confirming that the imported drug batch corresponds with the Marketing Authorisation of its country of origin and the CTA of the trial it is being imported for.

The original company approached to import OK432 were unable to perform QP release as the manufacturing company in China was unwilling to provide an official Certificate of Analysis and declined to undergo a formal laboratory inspection. Without these documents the QP was unable to complete their declaration.

Having explained this quandary to the MHRA, I worked closely with their import inspectors to clarify the essential information that was required for OK432 importation in the absence of an official Certificate of Analysis and formal laboratory inspection. An alternative import company was identified who were able to meet the modified MHRA requirements for QP release. Fortuitously, the QP for this company had prior experience working with the manufacturers of OK432 and had inspected their laboratories a year earlier for a previous client. This provided reassurance for all parties that the imported IMP would meet the standards necessary for UK usage.

Unfortunately, this process was time-consuming, and OK432 did not arrive in the respective pharmacies of the trial centres until 18 months after the initial HRA and MHRA approvals were granted. To lessen the impact of the delay, the design of TILT was amended from a two-arm trial (OK432 *vs* standard care) to a three-arm study (OK432 *vs* BCG *vs* standard care). The BCG and standard care arm opened as soon as the amendment was approved, and recruitment to these two arms occurred for 12 months before OK432 was obtained. Once OK432 was available, the third arm was opened, and the randomisation module altered to allow allocation to OK432.

4.2.3.1. Storage of OK432

According to the product information for OK432, it should be stored at temperatures below 10°C, but avoiding freezing. During importation from China, cold chain logistics were required to ensure these temperatures were maintained. Unfortunately, within two weeks of the product arriving in the UK, and after only one participant had received it, one trial site experienced a temperature excursion of the clinical trials fridge. Over three occasions, the temperature dropped below 0°C, to -6°C at the lowest point. Stability data was obtained from the manufacturer, following which the decision was made to destroy the affected stock.

By coincidence, this event coincided with a Trial Steering Committee meeting at which an urgent safety measure (USM) was declared based on adverse reactions in the two treatment arms. In response to the USM, a decision was made to include a reduced

dose regimen for both IMPs to attenuate the risk of side effects. Based on the reduced dose regimen and the recruitment estimates of each trial site, surplus OK432 stock was able to be transferred from an alternative site to the affected site, and the trial continued without delay.

4.2.2.9. Recruitment

Although the TwiC methodology was employed in the hope it would expedite recruitment by providing an existing cohort of research-active patients who could be screened for eligibility, there were certain elements of the design that created challenges to recruitment.

Two of the three trial sites involved in TILT were tertiary referral centres, with multiple active research studies underway. It is common for patients to be referred to these centres specifically for consideration of clinical trials. This practice is encouraged and trials are often publicised at clinical and academic meetings around the UK, inviting clinicians to refer willing patients to the relevant centre. However, this was not possible for TILT. To refer a patient to a tertiary centre, local clinicians must first discuss the trial with their patients and enquire whether they are willing to travel to the trial centre for further discussion and assessment. However, this would have undermined the fundamental premise of a TwiC, which requires control patients to be blind to the existence of the trial.

Another consideration regarding participants referred from other centres was that whilst patients may be willing to travel a significant distance to be screened for a trial, they may be disinclined to repeat the journey if they are not selected for that trial. Consequently, if they were allocated to be a cohort-based control in a TwiC, they may decline ongoing follow-up at the trial centre, causing differential attrition. For these reasons, recruitment to TILT was limited to the catchment area of each study centre, although it was recognised that this may have had an impact on recruitment.

1.2. Results

1.2.1. Participant characteristics

1.2.1.1. ASSESS-meso

At the time of writing (20/06/2020), 107 participants had enrolled in ASSESS-meso across eight study centres. Collectively, participants had completed 433 study assessment visits, ranging from 1 to 12 visits per individual. Forty-four participants (41.1%) had died, with a median survival time of 8.7 months from diagnosis (IQR 4.8-13.8). Data upload was complete for 91 participants, whose characteristics are shown in Table 4-1. During the TILT recruitment period, 43 people were participating in ASSESS-meso across the three recruiting sites.

1.2.1.2. TILT

Between 27/01/2018 and 31/11/2019, seven participants were successfully randomised for the TILT trial. Three were allocated to receive BCG, one to receive OK432 and three were designated as controls. All but one participant were male, all had epithelioid-type MPM and all were treatment-naive apart from one, who had received four cycles of

palliative cisplatin and pemetrexed chemotherapy. Participant characteristics are shown in Table 4-2.

1.1.1. Primary outcome – feasibility

4.3.2.1. Recruitment, attrition & data completeness

The pre-stated feasibility goal of recruitment rate >66% to time and target was not met. The planned sample size was 12, however, only seven participants were randomised during the 22-month trial recruitment period, yielding an overall recruitment rate of 58.3% of target. Furthermore, of seven participants randomised, two withdrew from the trial after randomisation; one who had been allocated to receive BCG and one who had been designated as control. This created an attrition rate of 28.6%, which breached the pre-specified feasibility criteria of <10%.

Data completeness was high. The main CRF, AM07 "Clinical Assessment", was completed in full for all participants for all study visits. A small number of data points were missing from CRFs AM08 "Blood tests" (38 missing values), AM09 "Imaging" (10 missing values) and AM11 "Symptom scores" (12 missing values). This resulted in a total of 60 missing values over 8750 data points, yielding a data completeness rate of 99.3%. This comfortably exceeded the feasibility criteria of >90% data completeness. However, it was noted that most of the missing data related to control participants, particularly at Visits two and three. It is possible that the TwiC methodological quirk that meant control patients were not explicitly participating in a trial caused confusion with regard to follow up data collection requirements.

		All participants
Total		91
Male		77 (84.6)
Age, median (range)		74 (33-93)
Performance status	0	30 (33.0)
	1	42 (46.2)
	2	17 (18.7)
	3	2 (2.2)
Asbestos exposure	None recalled	14 (15.4)
	Transient exposure	11 (12.1)
	Light/passive exposure	20 (22.0)
	Heavy/active exposure	46 (50.5)
Presenting symptoms	Breathlessness	72 (79.1)
	Chest pain	32 (35.1)
	Cough	38 (41.8)
	Sweats	12 (13.2)
	Lethargy	20 (22.0)
	Anorexia	11 (12.1)
	Weight loss	25 (27.5)
	Asymptomatic	3 (3.3)
Duration of symptoms	< 1 month	21 (23.1)
	1-3 months	39 (42.9)
	> 3 months	28 (30.8)
	Asymptomatic	3 (3.3)
Method of diagnosis	US-guided biopsy	10 (11.0)
	CT-guided biopsy	8 (8.8)
	Medical thoracoscopy	46 (50.6)
	VATS	16 (17.6)
	Other biopsy (e.g. laparoscopic)	5 (5.5)
	Cytological	4 (4.4)
	Clinico-radiological	2 (2.2)
Disease site	Pleural	88 (96.7)
	Peritoneal	3 (3.3)
Laterality	Left	38 (41.8)
	Right	50 (55.0
	Peritoneal	3 (3.3)
Tumour histology	Epithelioid	72 (79.1)
	Sarcomatoid	10 (11.0)
	Biphasic	2 (2.2)
	Deciduoid	1 (1.1)
	No histology obtained	6 (6.6)
Brims prognostic score	1 (best prognosis)	11 (12.1)
	2	33 (36.3)
	3	16 (17.6)
	4 (worst prognosis)	31 (34.1)

Table 4-1 - Baseline characteristics of participants enrolled in ASSESS-meso, as recorded on 27/02/2020. Abbreviations: CT – computed tomography; US – ultrasound; VATS – video-assisted thoracic surgery

	All participants	OK432	BCG	Control
Total	7	1	3	3
Male	6 (85.7)	-	3 (100)	3 (100)
Age, median (range)	73 (60-83)	64	71 (60-73)	80 (73-83)
Performance status 0	3 (42.9)	-	2 (66.7)	1 (33.3)
1	2 (28.5)	1 (100)	-	1 (33.3)
2	1 (14.3)	-	-	1 (33.3)
3	1 (14.3)	-	1 (33.3)	-
Asbestos exposure				
None recalled	1 (14.3)	1 (100)	-	-
Transient	1 (14.3)	-	-	1 (33.3)
Light/passive	1 (14.3)	-	1 (33.3)	-
Heavy/active	4 (57.1)	-	2 (66.7)	2 (66.7)
Presenting symptoms				
Breathlessness	5 (71.4)	1 (100)	2 (66.7)	2 (66.7)
Chest pain	1 (14.3)	-	1 (33.3)	-
Cough	3 (42.9)	-	2 (66.7)	1 (33.3)
Sweats	-	-	-	-
Lethargy	1 (14.3)	-	1 (33.3)	-
Anorexia	1 (14.3)	-	-	1 (33.3)
Weight loss	1 (14.3)	-	-	1 (33.3)
Asymptomatic	1 (14.3)	-	-	1 (33.3)
Duration of symptoms				
< 1 month	3 (42.9)	1 (100)	1 (33.3)	1 (33.3)
1-3 months	1 (14.3)	-	-	1 (33.3)
> 3 months	2 (28.6)	-	2 (66.7)	-
Not recorded	1 (14.3)	-	-	1 (33.3)
Method of diagnosis				
CT-guided biopsy	1 (14.3)	1 (100)	-	-
Medical thoracoscopy	5 (71.4)	-	3 (100)	2 (66.7)
VATS	1 (4.3)	-	-	1 (33.3)
Laterality Left	2 (28.6)	-	1 (33.3)	1 (33.3)
Right	5 (71.4)	1 (100)	2 (66.7)	2 (66.7)
Tumour histology				
Epithelioid	7 (100)	1 (100)	3 (100)	3 (100)
Previous treatment				
Chemotherapy	1 (100)	1 (100)	-	-
Radiotherapy	-	-	-	-
Surgery	-	-	-	-
Bevacizumab	-	-	-	-
Immunotherapy	-	-	-	-
Brims prognostic score				
1 (best prognosis)	1 (14.3)	-	-	1 (33.3)
2	5 (71.4)	1 (100)	3 (100)	1 (33.3)
3	-	-	-	-
4 (worst prognosis)	1 (14.3)	-	-	1 (33.3)

Table 4-2 Baseline characteristics of TILT participants. All values given are n (%) unless otherwise stated.

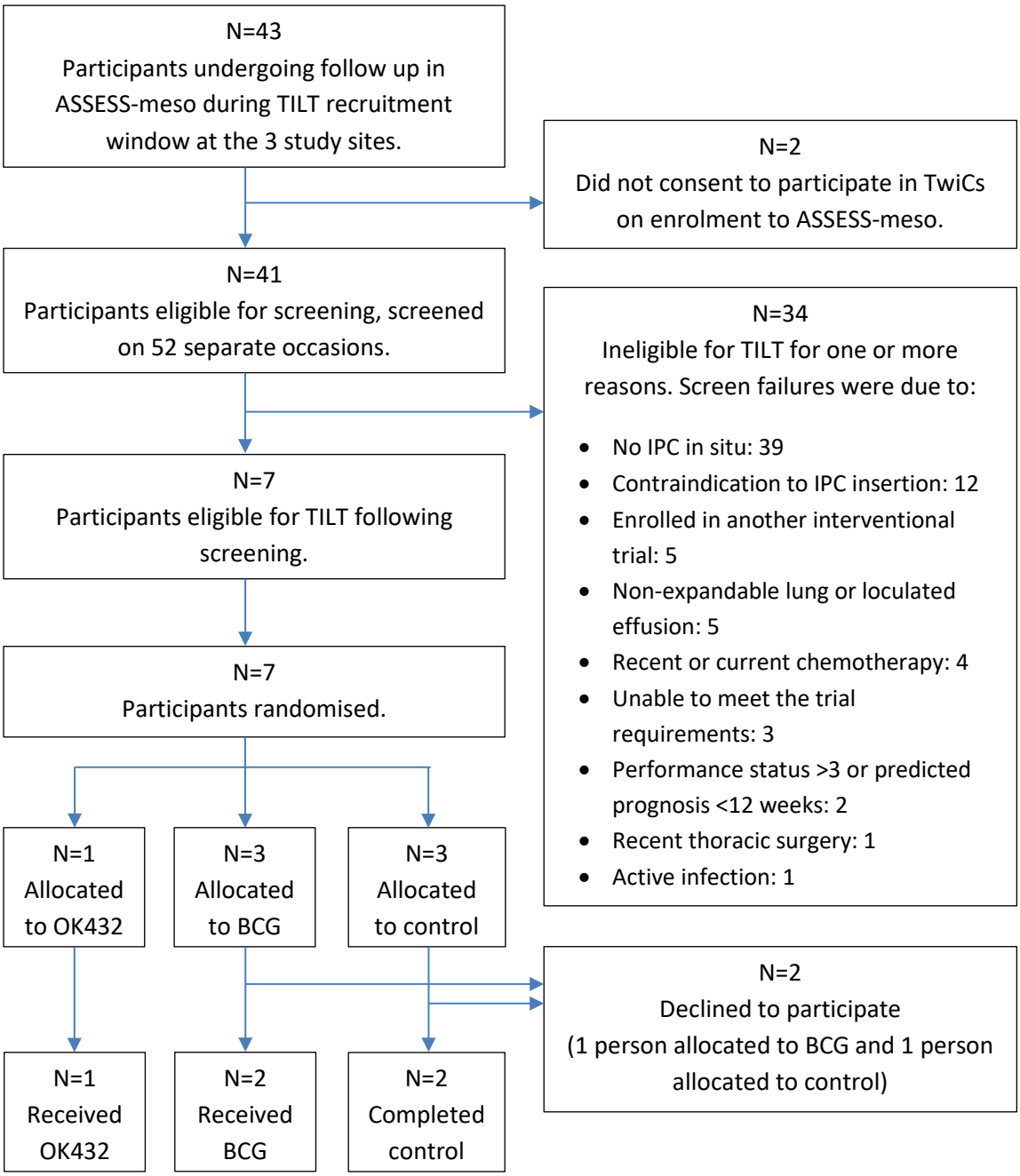


Figure 4.3 CONSORT diagram for TILT. IPC – indwelling pleural catheter, TwiC – trials within cohorts

Review of screening logs provided further information about the recruitment difficulties. Forty-three participants were undergoing follow-up in ASSESS-meso at the recruiting centres during the TILT enrolment period. Of these, two people had chosen not to

participate in TwiCs when they joined the cohort. The remaining 41 patients were screened for TILT eligibility on 52 occasions (eight patients were screened on two occasions and three patients were screened on three occasions, due to the dynamic nature of certain eligibility criteria over time, e.g. participants may have had an IPC inserted several months after diagnosis or may have completed chemotherapy and become eligible). The seven participants randomised for TILT were the only people to meet the eligibility criteria at any point (see Fig. 4.3).

The most frequent reason that patients were not eligible for TILT was the absence of a functioning IPC (cause of 39 screen failures), which often co-existed with a known contra-indication to IPC insertion (present at 12 screen failures). The presence of non-expandable lung with <50% pleural apposition on x-ray and/or a moderate or heavily loculated effusion was the cause of five screen failures. Five participants were enrolled in an alternative interventional trial at the time of screening (MARS2, ATOMIC-meso and CONFIRM) and were therefore ineligible for TILT, whilst four participants were ineligible due to recent or concurrent chemotherapy treatment. Nineteen patients had more than one reason for ineligibility.

In addition to screening existing ASSESS-meso participants, the research team also reviewed the eligibility of patients discussed at the regional mesothelioma MDT, hosted by North Bristol NHS Trust. A further 59 patients were discussed in this forum, the majority of whom were being treated at other hospitals in the region. Fifteen of these patients were potentially eligible for TILT based on the information available at MDT. Of

these, six did not wish to travel to the study site, four enrolled in an alternative trial and four deteriorated and/or died before they could be reviewed at the trial centre. One person attended North Bristol and was randomised.

The majority of patients deemed ineligible following MDT discussion had no pleural effusion, no IPC or had undergone pleurodesis (n=33). Of the remaining, three patients had underlying NEL, two were receiving chemotherapy and one received immunotherapy in the private sector. Three patients deteriorated before they could be enrolled in ASSESS-meso and two declined further hospital follow up.

4.3.2.2. Feasibility of the TwiC design

Certain features of the TwiC methodology rendered it unfeasible for use in mesothelioma populations. Specifically, a large proportion of participants declined to participate in the trial after randomisation (2/7; 28.6%) and all patients in the control arm had been unblinded to the existence of the trial prior to randomisation (3/7; 100%). Other aspects of the design, however, were feasible. For example, most people who enrolled in ASSESS-meso were willing to be screened and randomised for TwiCs (87/91; 95.6%). Similarly, the TwiC methodology was considered acceptable by TILT participants and their family members when it was described to them during qualitative interviews on completion of the trial (described in full in Chapter 5). The remainder of this section will focus on each feasibility outcomes in turn.

4.3.2.2.1. Attrition after randomisation

Two patients declined to participate in TILT after randomisation; one who was allocated to receive BCG and one who was allocated to control. Qualitative interviews with these participants and their family members provided insight into this decision and more information is provided in Chapter 5. Broadly speaking, however, patients wished to prioritise quality of life and were concerned that participating in the trial may have compromised this. The patient allocated to BCG was reluctant to receive a trial medication that carried a risk of side effects, whilst the patient allocated to control did not wish to return to hospital as frequently as the trial schedule required. Importantly, both patients had agreed to be considered for randomised trials on enrolment in ASSESS-meso and both remained keen to be considered for future TwiCs, even after choosing not to participate in TILT.

Clearly patients need to know the specific requirements of a trial before they can decide whether they wish to participate. With a standard RCT, this happens at the outset, as participants are provided with a trial PIS prior to enrolment. However, with the TwiC methodology, eligible participants are randomised prior to receiving any information about the trial, creating the possibility of post-randomisation attrition. Since it is impossible to provide information about every potential TwiC on enrolment to the cohort (and the volume of information received by patients would be unmanageable), it is likely that there will always be a proportion of people who choose not to participate in any given TwiC after they have been randomly selected to participate. Post-randomisation attrition could render the trial underpowered or introduce bias if attrition were unequal between arms.

4.3.2.2.2. Blinding of controls

A key element of the TwiC design is that control participants remain unaware of the existence of the trial, therefore, as part of the feasibility evaluation, participants in TILT were asked whether they were aware of the trial prior to randomisation. All seven participants stated that they had prior knowledge of TILT, with some control patients explicitly asking members of the trial team "Am I participating in TILT?" during research visits. It was, therefore, impossible to maintain blinding of the control arm and this meant that many of the potential benefits of the TwiC design were lost.

The mechanism through which participants had been unblinded to TILT were explored during qualitative interviews. Interestingly, three participants had been involved in PPI groups at which TILT was discussed, months before the trial design was finalised. Two participants had become aware of TILT after hearing other patients discussing it at local mesothelioma support groups. Two participants had been told about TILT by clinicians at non-trial centres who knew about the trial but were unaware of the specific requirement for blinding. One of these patients was the gentleman who withdrew after being allocated to the control arm. He had been referred to the trial centre to be considered for TILT and did not wish to return once he knew he was not receiving the intervention. This would not have occurred if a standard, double-blind RCT design had been used.

Attempts to blind patients to the existence of a trial also contributed to the recruitment difficulties. The trial was deliberately not publicised on resources such as the Cancer Research UK Clinical Trial Database and Mesothelioma UK's Clinical Trial Spreadsheet,

nor was it promoted at national respiratory research events such as the UK Pleural Society Annual Research Update Day. Inevitably this reduced the number of potential participants referred to trial sites from other centres.

Attempts to maintain blinding also meant that potentially eligible participants identified at the regional mesothelioma MDT were not informed about TILT when they were invited to attend the study centre. It is unknown whether the seven patients who chose not to travel to Bristol would have attended had they been told about TILT or provided with a PIS, however it must be a consideration when reviewing the recruitment challenges faced by the trial.

4.3.2.2.3. Willingness to be considered for TwiCs

The majority of participants who enrolled in ASSESS-meso were willing to be screened and randomised for future TwiCs. Only four out of 91 (4.4%) participants did not wish to be considered for future trials. The characteristics of these participants are shown in Table 4-3. Patient numbers were too small to perform statistical comparisons, however there were no overt differences between patients who chose not to be considered for future TwiCs and the overall ASSESS-meso study population. Interestingly, all four patients who declined TwiCs were enrolled at the same study site, raising the possibility that the TwiC concept was presented differently to participants at that centre.

		Participants who did not wish to be considered for TwiCs	All ASSESS-meso participants
Total		4	91
Male		3 (75)	77 (84.6)
Age, median (range)		79 (64-93)	74 (33-93)
Performance status	0	2 (50)	30 (33.0)
	1	2 (50)	42 (46.2)
	2	-	17 (18.7)
	3	-	2 (2.2)
Asbestos exposure	None recalled	-	14 (15.4)
	Transient	-	11 (12.1)
	Light/passive	3 (75)	20 (22.0)
	Heavy/active	1 (25)	46 (50.5)
Presenting symptoms	Breathlessness	2 (50)	72 (79.1)
	Chest pain	1 (25)	32 (35.1)
	Cough	3 (75)	38 (41.8)
	Sweats	1 (25)	12 (13.2)
	Lethargy	-	20 (22.0)
	Anorexia	-	11 (12.1)
	Weight loss	1 (25)	25 (27.5)
	Asymptomatic	1 (25)	3 (3.3)
Duration of symptoms	< 1 month	2 (50)	21 (23.1)
	1-3 months	1 (25)	39 (42.9)
	> 3 months	1 (25)	28 (30.8)
	Asymptomatic	-	3 (3.3)
Method of diagnosis	US-guided biopsy	1 (25)	10 (11.0)
	CT-guided biopsy	-	8 (8.8)
	Medical thoracoscopy	2 (50)	46 (50.6)
	VATS	-	16 (17.6)
	Other biopsy (e.g. laparoscopic)	-	5 (5.5)
	Cytological	1 (25)	4 (4.4)
	Clinico-radiological	-	2 (2.2)
Disease site	Pleural	4 (100)	88 (96.7)
	Peritoneal	-	3 (3.3)
Laterality	Left	2 (50)	38 (41.8)
	Right	2 (50)	50 (55.0
	Peritoneal	-	3 (3.3)
Tumour histology	Epithelioid	3 (75)	72 (79.1)
	Sarcomatoid	-	10 (11.0)
	Biphasic	-	2 (2.2)
	Deciduoid	-	1 (1.1)
	No histology obtained	1 (25)	6 (6.6)
Brims prognostic score	1 (best prognosis)	2 (50)	11 (12.1)
	2	1 (25)	33 (36.3)
	3	1 (25)	16 (17.6)
	4 (worst prognosis)	-	31 (34.1)

Table 4-3 Characteristics of ASSESS-meso participants who chose not to be considered for future TwiCs

4.3.2.2.4. Acceptability of the TwiC design

The TwiC design was explained to trial participants and their family members during qualitative interviews, performed once they had completed trial follow up (see Chapter 5). The TwiC design was acceptable to participants and their relatives and, specifically, no-one expressing concerns about controls being "deceived". Participants' and relatives' views varied as to whether the TwiC methodology was preferable to a blinded, placebo-controlled trial, but overall it was considered an acceptable approach to clinical trials in MPM.

The qualitative interviews were performed alongside TILT, i.e. each participant was interviewed soon after their final trial visit. Contemporaneous analysis of the qualitative data enabled modifications to be made to the trial protocol to improve overall acceptability. Specific changes were made after the first participant received BCG. This participant reported feeling abandoned when he experienced an adverse reaction after the IMP administration:

> *"I think [that] was the start of the point where we felt really alone, really alone." Participant 32-6T, 71-year-old male.*

On his suggestion, daily telephone check-ups were initiated in the week after IMP administration. An extra safety visit was introduced at day 3 to ensure that participants were closely monitored and felt supported. Finally, because that participant's reaction had occurred over a weekend, it was recommended to all trial sites that the IMP be administered at the beginning of the week, to allow regular checks to happen during

normal working hours and to reduce the risk of an adverse reaction occurring out of hours. These changes were well-received, as described by a subsequent participant:

> *"I thought the more I see you, the better I am going to be, was my sort of idea." Participant 104-1T, 61-year-old male.*

Specifically, the additional visits were not considered to be overly burdensome.

> *"Interviewer: [What about] the frequency of the trial visits? Were they a problem at all?*
>
> *Participant: No, not a problem at all. Well, as I am retired, I don't find it a problem… I didn't find it any problem coming down here at any time of day because I have got nothing else to do."*
>
> *Participant 104-1T, 61-year-old male.*

1.1.2. Secondary outcomes

4.3.3.1. Adverse events

4.3.3.1.1. Non-haematological adverse events

A total of eight non-haematological adverse events occurred during the trial, affecting five participants. There were three SAE, affecting one person in each arm of the trial. There were no grade four or five AE and no deaths related to AE (see Table 4-4).

The most common AE was a systemic inflammatory response syndrome, consisting of pyrexia, malaise, increased breathlessness and fatigue that occurred within 72 hours of

IMP administration. This affected all three participants who received OK432 or BCG and resulted in admission to hospital for the first two patients. In both cases, symptoms settled with analgesia and antipyretics and the patients were discharged within three days. One patient (who received BCG) experienced a recurrence of low-grade fever and fatigue some days after being discharged from hospital. These symptoms persisted for several weeks but eventually resolved following treatment with an oral steroids.

In response to this, the data monitoring committee passed a USM recommending the use of a lower dose of BCG and OK432. The USM also recommended three days of anti-inflammatory and anti-pyretic medication to be given after IMP administration and introduced an additional safety visit at 72 hours post-IMP administration, as suggested by participant 32-6T. The next participant to receive BCG was treated in accordance with the USM and experienced a milder inflammatory response that did not require admission to hospital.

	OK432	BCG	Control
Any adverse event	1	3	4
Grade 1	-	-	2
Grade 2	-	1	1
Grade 3	1	2	1
Grade 4/5	-	-	-
Serious adverse event	1	1	1
Specific events:			
Systemic inflammatory response	1	3	-
Pleural infection	-	-	2
Chest wall pain	-	-	1
Upper respiratory tract infection	-	-	1

Table 4-4 Non-haematological adverse events according to treatment allocation

One patient experienced pleural infection related to their IPC. This patient was in the control arm of the trial. They were initially managed as an outpatient with oral antibiotics, however this failed to control the infection, so the patient was admitted to hospital for intravenous antibiotics and free drainage of the pleural space. This treatment was successful.

4.3.3.1.2. Haematological adverse events

Participants randomised to receive an IMP experienced a peak in CRP at visit one (the first visit after IMP administration) whilst control participants did not (mean CRP 200 for IMP group; 95% CI 74.4-325.6 *vs* mean CRP of 14 for controls; 95% CI -22.0-50.0; p0.032 - Fig 4.4). Two-way ANOVA demonstrated a strong relationship between serum CRP and receipt of IMP ($F_{(1, 15)}$=9.95; p=0.007) as well as serum CRP and trial visit ($F_{(3, 15)}$=4.81; p=0.015). There was a meaningful interaction between receipt of IMP and trial visit on serum CRP ($F_{(3, 15)}$=7.22; p=0.003), with the greatest effect of IMP seen at visit one (correlation coefficient 207.17; 95% CI 107.5-306.9; p<0.001).

Serum platelets also rose at Visit one in people randomised to receive OK432 or BCG, whilst remaining relatively static in control participants (mean platelets for IMP group 588.3; 95% CI 323.0-853.7 *vs* mean platelets for controls 240.5; 95% CI 178.1-302.9; p=0.043 - Fig 4.5). Two-way ANOVA confirmed an association between IMP allocation and trial visit on serum platelets ($F_{(1, 15)}$=6.31; p=0.024), however this relationship was lost on multiple regression modelling (correlation coefficient 175.1; 95% CI -59.5-409.7; p=0.132).

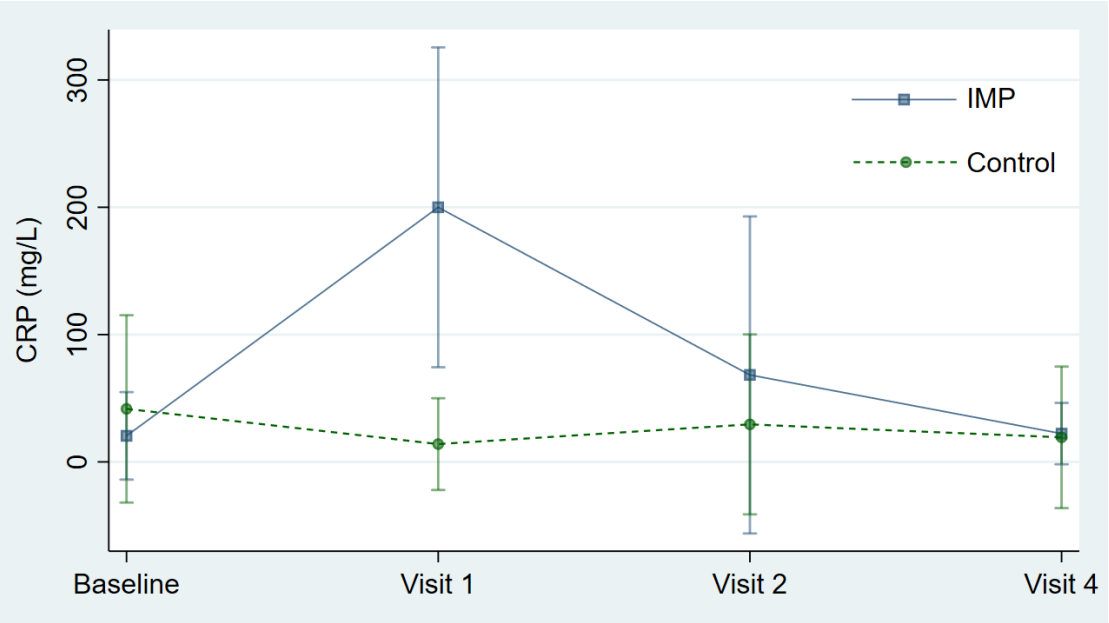


Figure 4.4 Mean CRP and 95% confidence intervals of patients randomised to receive OK432 or BCG (IMP group) compared with controls at each trial visit.

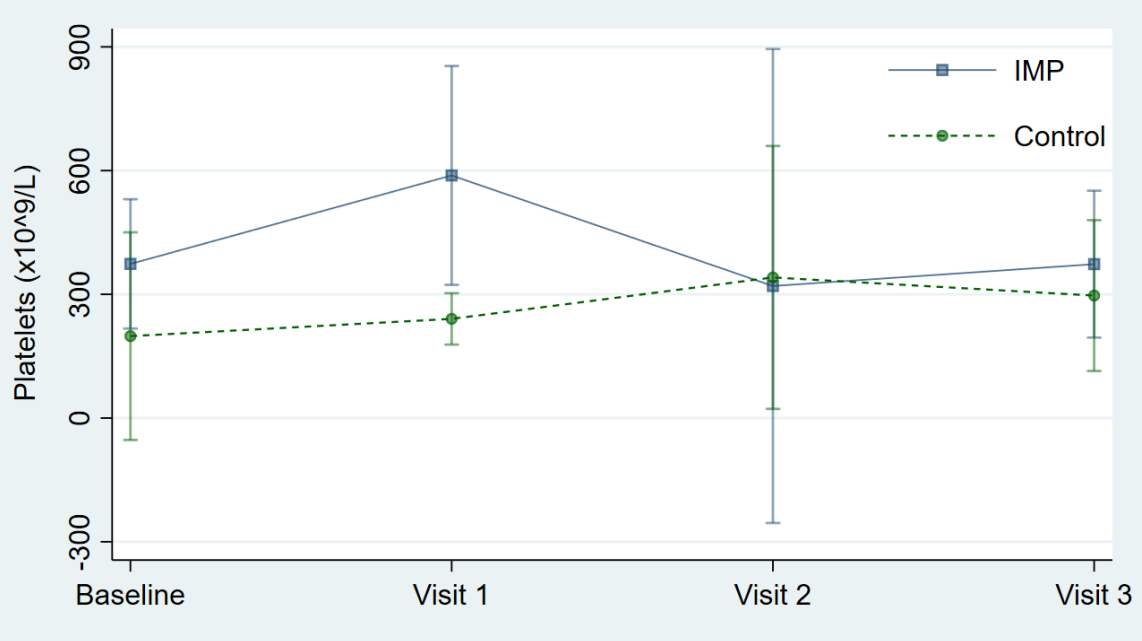


Figure 4.5 Mean platelet values and 95% confidence intervals of participants randomised to receive OK432 or BCG (IMP group) compared with controls at each study visit.

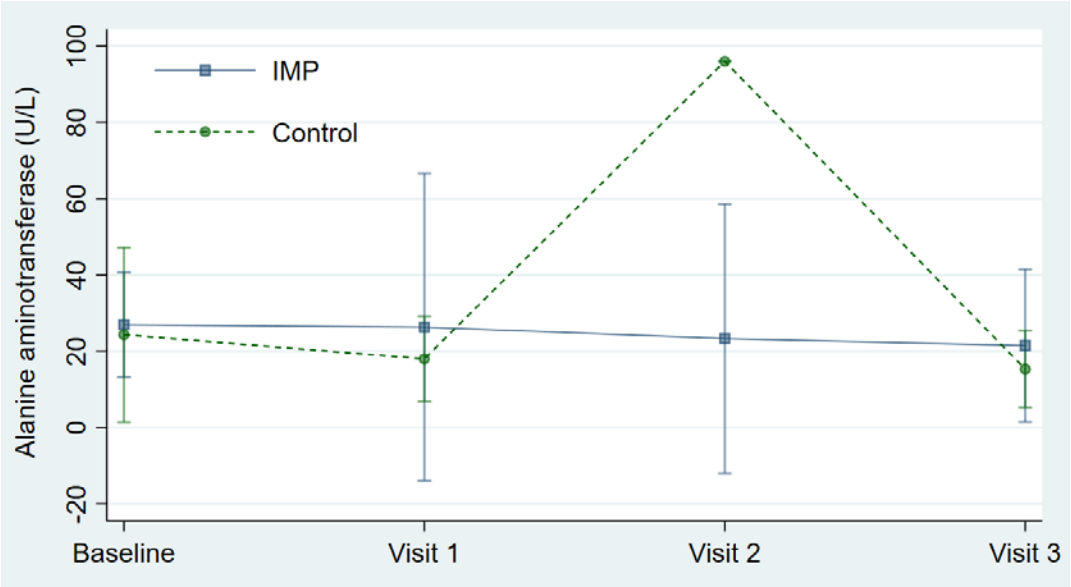


Figure 4.6 Mean alanine aminotransferase and 95% confidence intervals for patients randomised to receive OK432 or BCG compared with controls at each study visit

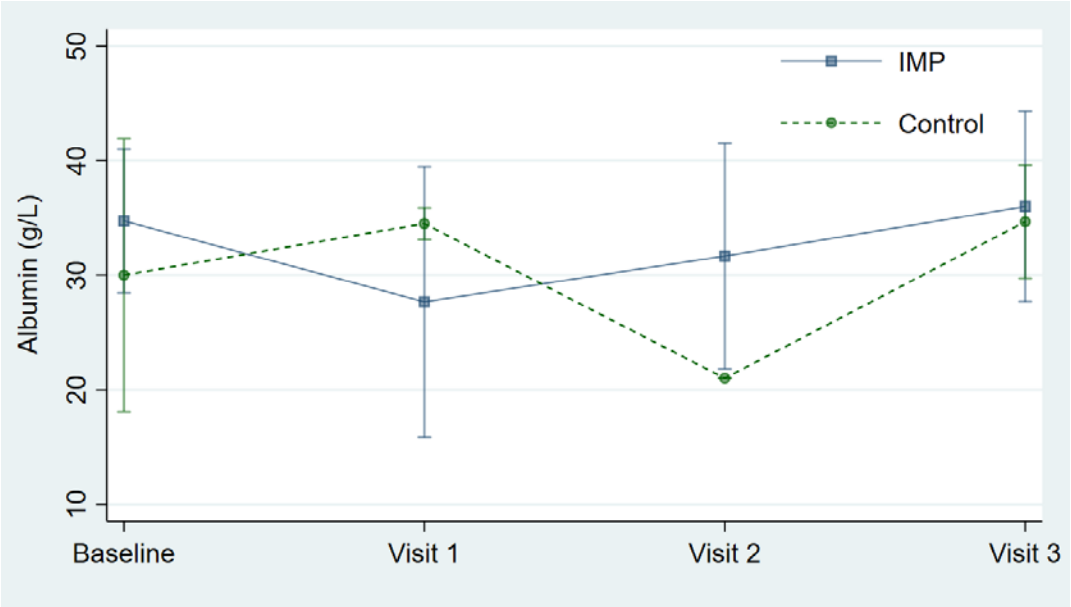


Figure 4.7 Mean albumin levels with 95% confidence intervals for patients randomised to receive an IMP compared with controls at each study visit.

Alanine aminotransferase and albumin were abnormal in control participants at visit two compared to people in the IMP group (Figs 4.6 and 4.7 respectively). However, on inspection of the data, only one control participant contributed liver function test data

at that timepoint, so the observed difference between groups was solely due to that person. He had been treated for pleural infection one week previously, which was the likely cause of his raised ALT and reduced albumin.

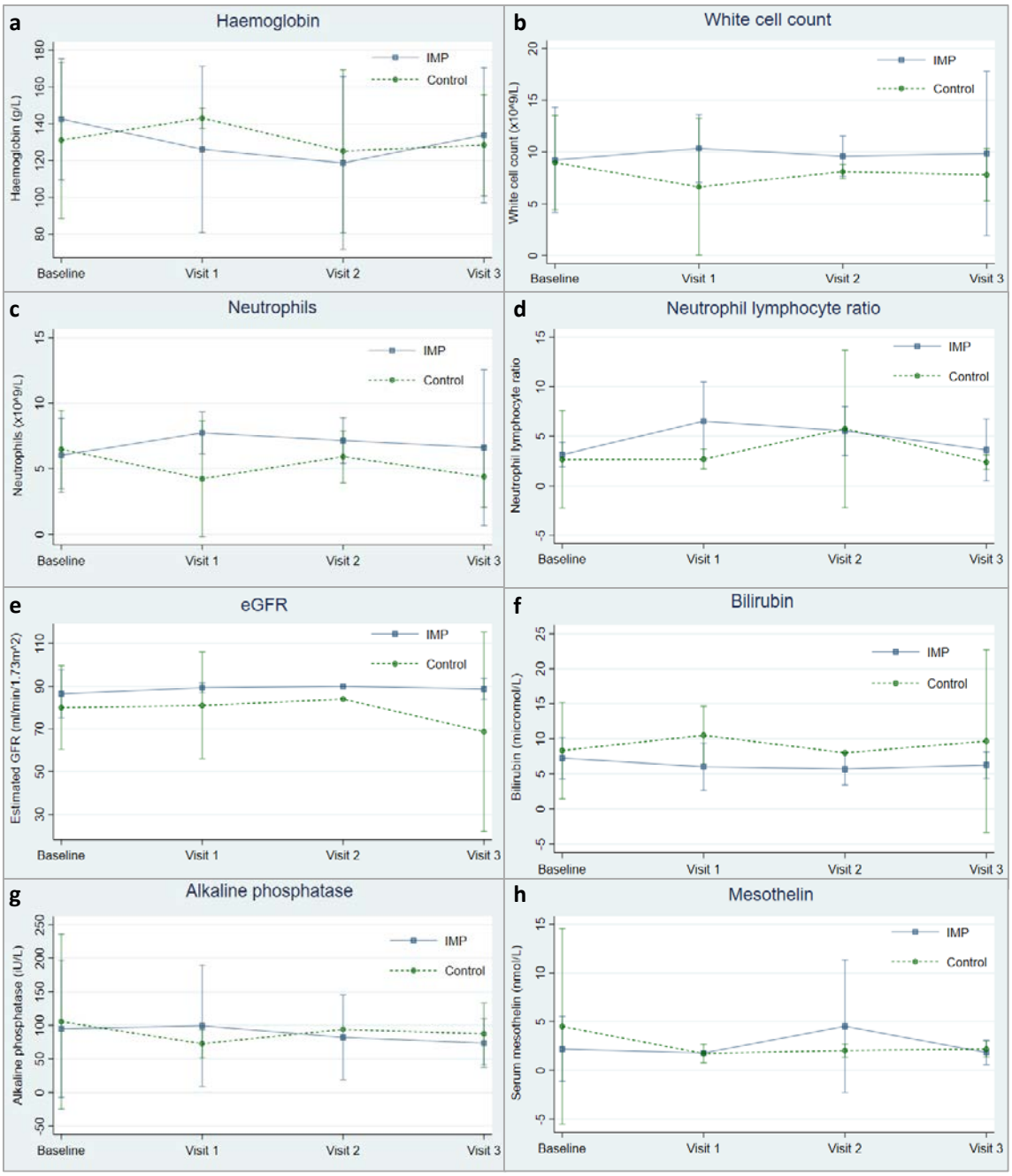


Figure 4.8 Mean results for (a) haemoglobin, (b) white cell count, (c) neutrophils, (d) neutrophil lymphocyte ratio, (e) estimated GFR, (f) bilirubin (g) alkaline phosphatase (h) mesothelin) with 95% confidence intervals for patients randomised to receive an IMP compared with controls at each study visit.

There was no difference in haemoglobin, white blood cell count, neutrophil count, neutrophil lymphocyte ratio, glomerular filtration rate (GFR), bilirubin, alkaline phosphatase or mesothelin between participants randomised to receive an IMP and those in the control arm over the trial visits (Fig 4.8).

4.3.3.2. Pleural fluid drainage volumes and pleurodesis rates

The absolute volume of fluid drained from participants' IPCs at each community drainage ranged from 0mls to 1500mls. The average amount of fluid drained each time was 436.7mls (median 353.6, IQR 1-741.7). Participants randomised to receive OK432 or BCG experienced a steady decline in the average volume of pleural fluid drained since the previous trial visit, whilst control participants' drainage volumes were stable over the trial period (Fig 4.9).

On linear regression, there was a trend towards a negative association between trial visit and IPC drainage volume in people randomised to receive an IMP (unadjusted correlation coefficient for visit two -949.8; 95% CI -2020 to 120.9; p=0.077 and for visit three -1096.9; 95% CI -2340.1 to 146.2; p=0.078), however this association was not present on ANOVA modelling ($F_{(3,11)}$=2.04; p=0.167).

Six out of seven participants (85.7%) achieved pleurodesis and all six had their IPCs removed as a result. Median time from randomisation to pleurodesis was 42 days (IQR 30-132 days). People randomised to receive an IMP were no more likely to achieve

pleurodesis than control participants and there was no difference in time to pleurodesis between the groups (HR 0.35; 95% CI 0.06-2.13; p=0.255).

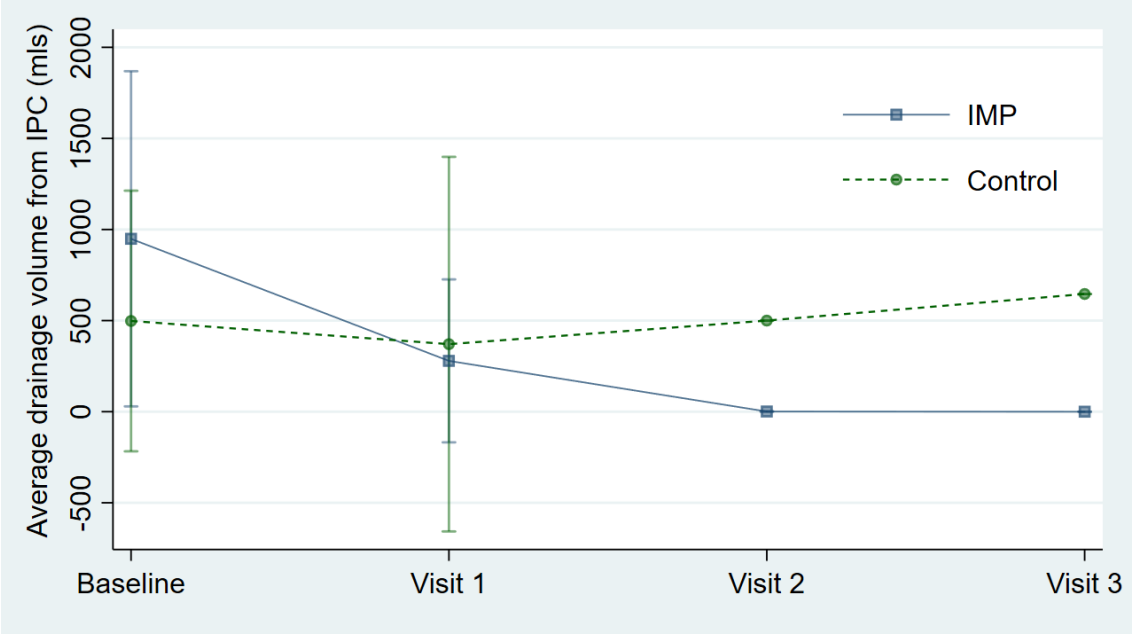


Figure 4.9 Average IPC drainage volumes (mean & 95% confidence intervals) at each trial visit for participants randomised to receive OK432 or BCG and controls.

4.3.3.3. Radiological response rates & survival

No partial or complete radiological responses were seen on CT scans at the end of TILT compared with baseline CT imaging. Three participants (42.9%) had progressive disease and four had stable disease (57.1%). There was no difference in radiological outcomes in people randomised to receive an IMP and those allocated to control (Table 4.5, p=0.486).

Survival status was reviewed on 02/06/2020; four patients were alive and three had died, with a minimum follow up of 8.9 months for living patients (range 8.9-45.0, median 25.0). Overall median survival was 21.0 months (IQR 8.9-29.0) with a 1-year

survival rate of 71.4% (5/7). There was no difference in median survival between participants randomised to receive OK432 or BCG (18.1 months; IQR 12.1-23.3) and control participants (29.0 months; IQR 5.2-45.0) with an unadjusted HR of 2.1 (95% CI 0.2-24.5; p=0.563) and an adjusted HR of 1.7 (95% CI 0.1-31.0; p=0.731).

	OK432 or BCG n (%)	**Control n (%)**
Complete/ partial response	-	-
Stable disease	3 (75%)	1 (33%)
Disease progression	1 (35%)	2 (66.7%)

Table 4-5 Radiological responses on end of trial CT scans compared to baseline CT

Survival for all participants compared favourably with national figures, even allowing for the fact that all TILT participants had epithelioid histology. The 2018 National Lung Cancer Audit for Mesothelioma (reporting data from 2014 to 2016) quoted a median survival of 13.1 months (IQR 6.5-23.3) for people with epithelioid MPM.(210) Recent open-label, phase II trials of immunotherapy in similar cohorts of MPM patients reported median survival of 16·6 months (95% CI 13·1–20·1) in patients treated with durvalumab and tremelimumab (NIBIT-meso-1), and 15·9 months (95% CI 10·7–not reached) in people given ipilimumab and nivolumab (MAPS2).(17, 82) The similarity between these trials and TILT survival outcomes is more likely to be a reflection of survivorship and selection bias in the TILT population than a true effect of immunotherapy.

4.3.3.4. *Patient-reported outcome measures*

Overall patients rated their symptoms as relatively low severity and reported reasonably good QoL. Breathlessness was the most troublesome symptom, with a median VAS score of 18.3 (range 0-36, IQR 8.3-25), where zero represented no breathlessness at all and 100 was the worst breathlessness imaginable. Chest pain (median 4.7, range 0-11.2, IQR 1.5-11.2) and sweats (median 2.2, range 0-14.5, IQR 0.3-7.9) were reportedly less severe. Median QoL score was 80 (range 66.7-90, IQR 76.9-81.7), where 0 was the worst health imaginable and 100 the best.

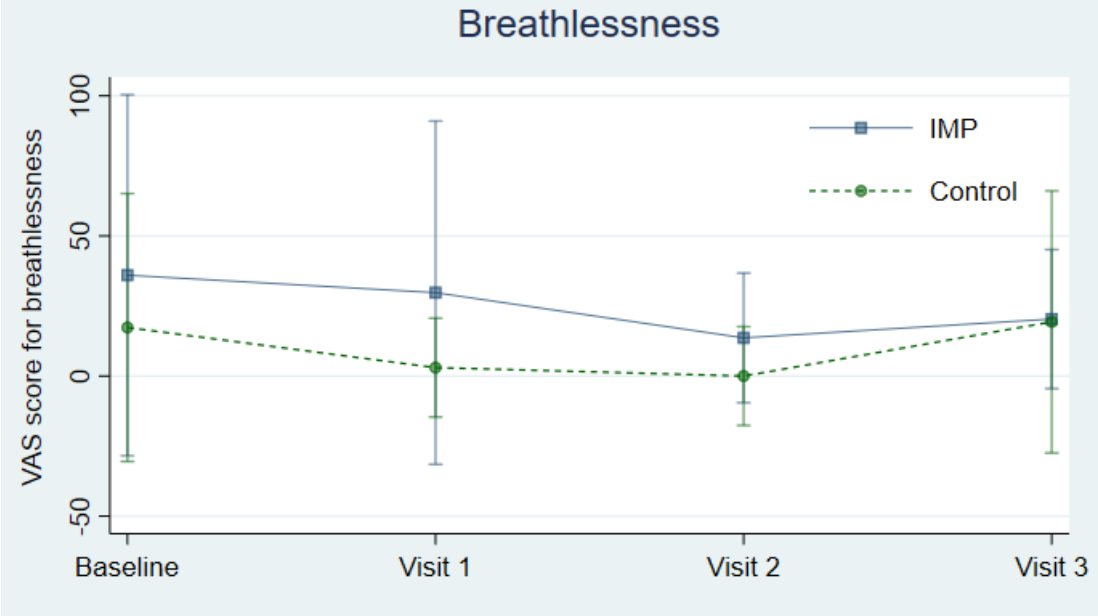


Figure 4.10 Patient reported symptom scores (mean and 95% confidence intervals) for breathlessness in people randomised to receive OK432 or BCG compared with controls at each study visit

There was no difference between the trial arms in patient-reported symptom scores for breathlessness (Fig 4.10), chest pain (Fig 4.11), sweats (Fig 4.12) or QoL (Fig 4.13) at each visit. Nor was there any difference in change in symptom scores over time, using

absolute values for maximum change and relative values, adjusted for baseline scores (two-way ANOVA analyses, all p values > 0.05).

Figure 4.11 Patient reported symptom scores (mean and 95% confidence intervals) for chest pain for people randomised to receive OK432 or BCG compared with controls at each study visit

Figure 4.12 Patient reported symptom scores (mean and 95% confidence intervals) for sweats in people randomised to receive OK432 or BCG compared with controls at each study visit

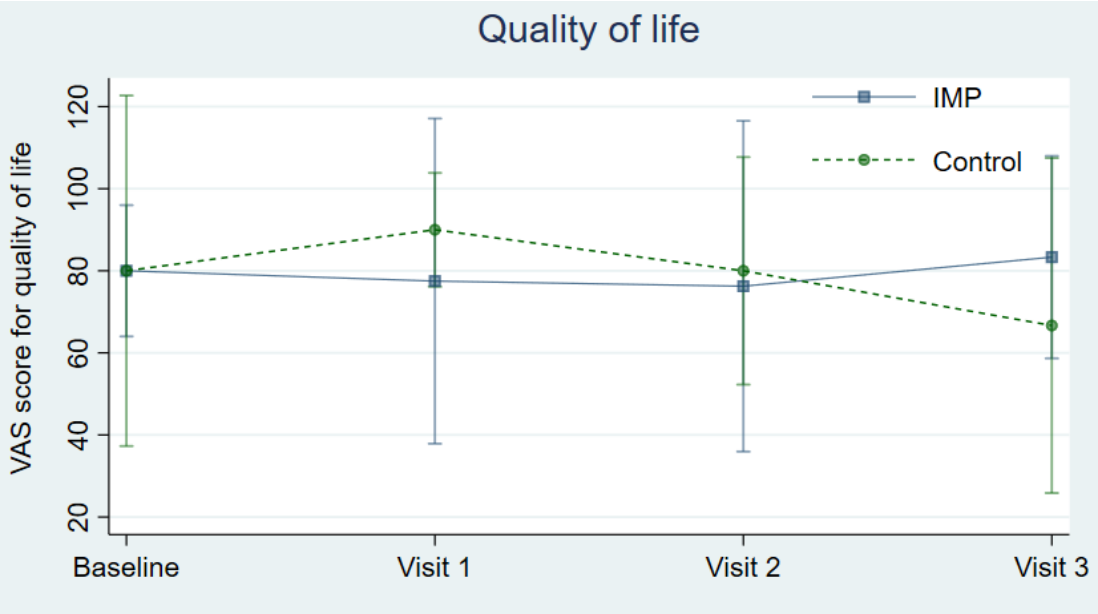


Figure 4.13 Patient reported symptom scores (mean and 95% confidence intervals) for quality of life in people randomised to receive OK432 or BCG compared with controls at each study visit

Daily VAS scores were only collected on participants who received an IMP. Two participants experienced a rise in breathlessness following IMP administration, whilst one was minimally breathless throughout. Breathlessness resolved within 10 days for one participant, whilst for the other it became more severe and persisted for the 21-day monitoring period (Fig 4.14). A similar pattern was seen for chest pain (Fig 4.15). Sweats occurred later, approximately five to seven days after the IMP was administered and were both more severe and longer-lasting (Fig 4.16).

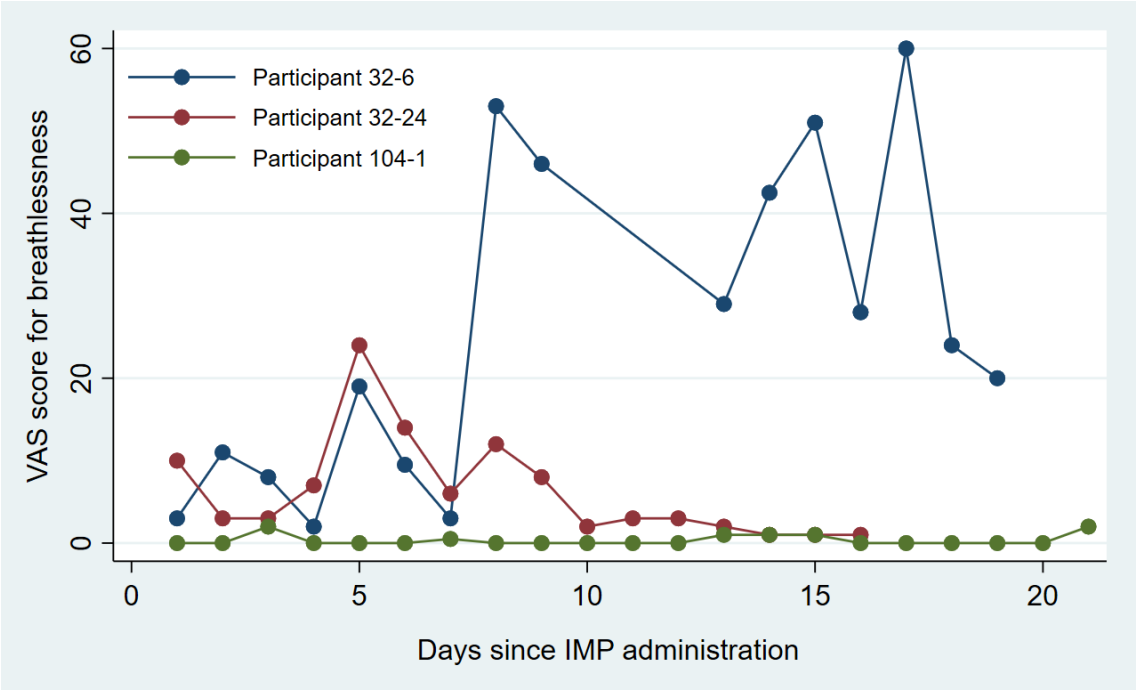


Figure 4.14 Daily VAS scores for breathlessness in people who received an IMP for the 21 days following IMP administration

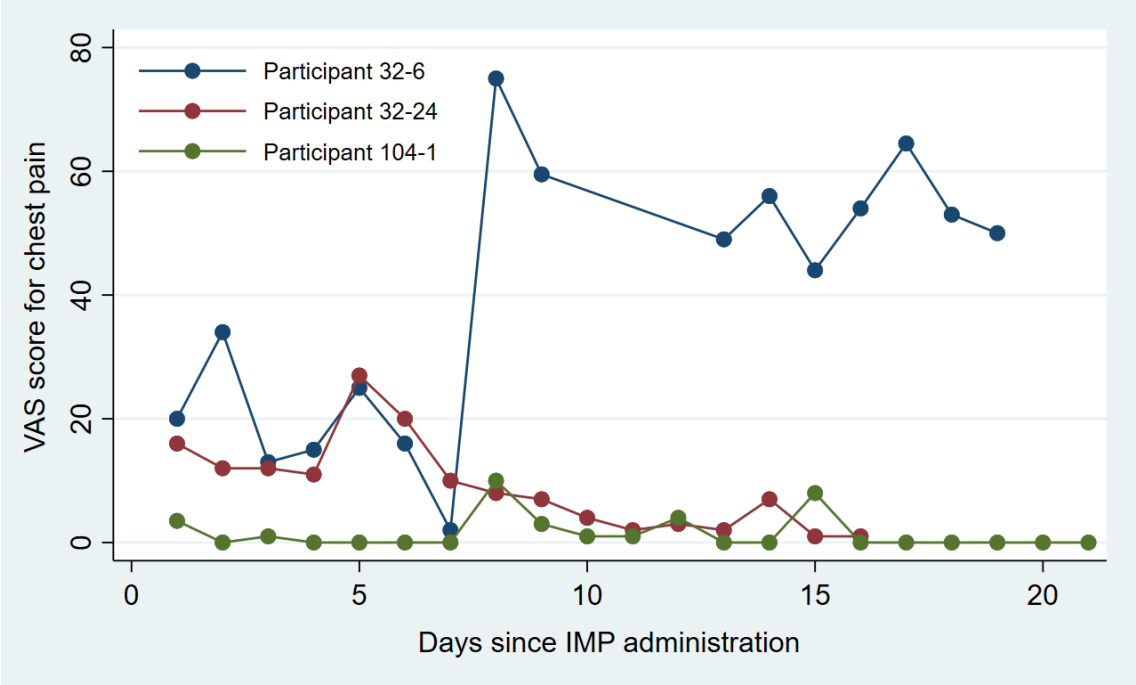


Figure 4.15 Daily VAS scores for chest pain in people who received an IMP for the 21 days following IMP administration

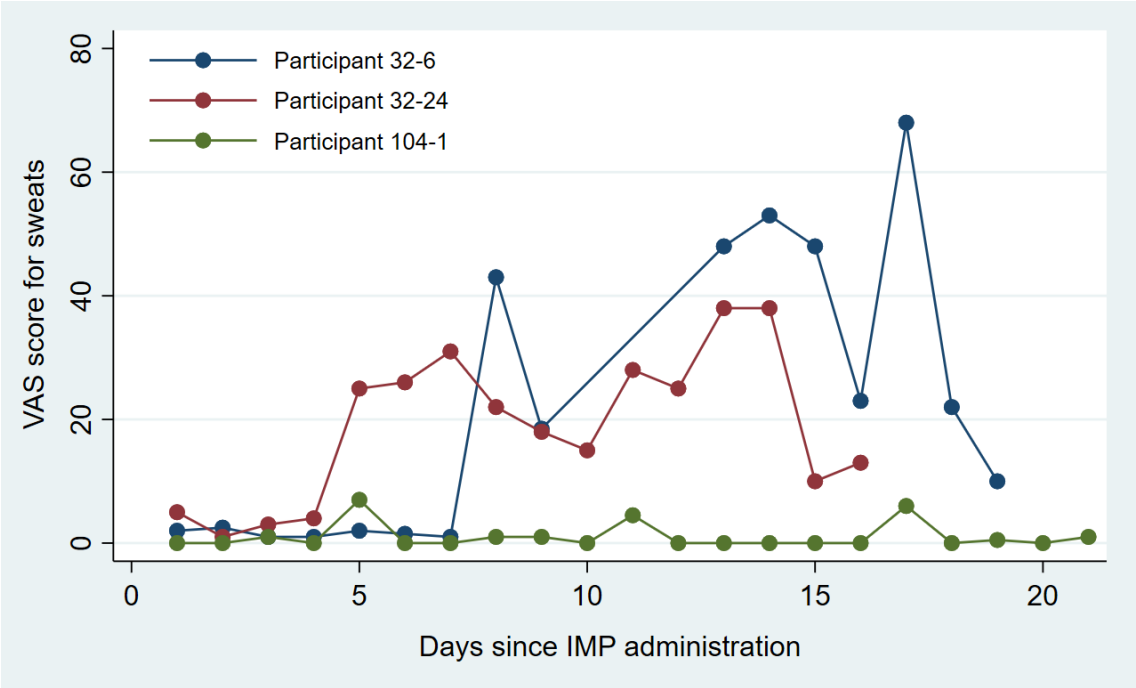


Figure 4.16 Daily VAS scores for sweats in people who received an IMP for the 21 days following IMP administration

1.2. Summary of findings

TILT was the first trial to apply the TwiC methodology to a CTIMP. We demonstrated that it was possible to adhere to the necessary clinical trial regulations and maintain ethical standards of informed consent and transparency using this design, and thus obtain the requisite approvals from the Research Ethics Committee, the HRA and the MHRA. Additionally, the trial design and processes were acceptable to participants and their relatives, with no participants or relatives expressing concerns about deception when the design was described to them during qualitative interviews.

Although it was feasible to design and conduct a CTIMP TwiC, it was not feasible to use the TwiC methodology to conduct a trial of intra-pleural immunotherapy in people with MPM. TILT failed to recruit to time and target, partly due to fewer eligible patients than predicted and partly due to specific elements of the TwiC design. Additionally, post-randomisation attrition was an issue, and this could cause bias if a similar phenomenon occurred in a full-scale trial. Finally, it was not possible to maintain blinding of control participants to the existence of the trial. This undermined one of the key features of the TwiC methodology and negated the intended benefit of reducing disappointment in control participants. In light of these findings, any future full-scale trial of intra-pleural immunotherapy in MPM should not be based on the TwiC design. Potential modifications to the method that could avoid the problems experienced in TILT, whilst maintaining some of the benefits associated with TwiCs, are discussed in Chapter 6.

Chapter 5 - Qualitative study

2.1. Background

MPM carries a significant physical, psychological and social burden. In her qualitative interviews with people with MPM, Dr Helen Clayson identified certain specific physical issues arising as a result of the occupational nature of the disease.(174) Many patients described experiencing a rapid deterioration in health and fitness, which was challenging for them to accept, as people who had previously relied on their strength for work and, often, their sense of self.(174)

Psychologically, Lebovitz et al described the anticipatory anxiety reported by people with MPM who had seen friends and colleagues die of the disease and had spent many years awaiting their own diagnosis.(211) This was described as the "Damocles Syndrome" by Barak and colleagues, who interviewed current and prior asbestos workers and found anticipatory anxiety was commonplace.(212) Expectation of a future diagnosis meant that when the diagnosis of MPM was confirmed it was often met with "stoical fatalism" and a sense of inevitability.(211, 212) Despite this, interviews also highlighted that many people experienced depression on receiving the diagnosis, as well as anger.(213, 214) Some patients struggled to process these emotions whilst simultaneously dealing with the burden of medical interventions.(213-215)

Socially, people with MPM described feeling isolated and mourned the loss of their jobs and ability to "contribute".(214) The legal ramifications of MPM as a prescribed disease, for which compensation was payable, were also challenging. Many people with MPM considered themselves self-reliant and were uncomfortable with the idea of claiming

damages or benefits, as doing so challenged their sense of independence and self-sufficiency.(174)

Although the experience of MPM is well researched, it is not clear how patients view taking part in MPM research. Considering the physical, psychological and social challenges of living with this condition, it would be understandable if people with MPM were reluctant to participate in trials. Trial participation inevitably places greater physical demands on people as they are required to attend appointments more frequently. Additionally, trial medication may cause side effects. This may require people to have to rely on others to look after them during this period – something which may not sit comfortably with the stoical and self-reliant nature of many people with MPM.

The limited prognosis associated with MPM could also create challenges for trial participation. Numerous studies have acknowledged the difficulty of recruiting people with incurable or palliative conditions to trials.(216-218) However, the same studies found that patients were often interested in research and could have benefited from participation.(218) Qualitative methods can be useful in clinical trial settings to help understand participants' experiences and to identify potential recruitment barriers.(170, 219)

Inviting people with terminal diagnoses to participate in clinical trials can introduce uncertainty and stress. Specifically, a trial may create tension between the prognostic

certainty associated with having an incurable disease and the uncertainty inherent in a trial.(220) Clearly, the fact of having an incurable cancer such as MPM is associated with great distress. However, for many people, especially those who have been living with anticipatory anxiety for several years, there may be some relief in the certainty of a confirmed diagnosis. Participation in research introduces uncertainty related to the potential therapeutic effects of the intervention and the possible risks and negative consequences of treatment. The possibility that the trial intervention may extend survival or even induce remission further undermines the pre-existing prognostic certainty.(220) This uncertainty can generate stress and anxiety and, if experienced for prolonged periods of time, may undermine people's sense of identity and disrupt their self-perception.(221)

Is the discomfort of uncertainty, albeit associated with the potential for an improved prognosis, worth abandoning the security of an inevitably dire situation for? The qualitative interviews aimed to gain insight into this question and other elements of clinical trial participation in people with MPM.

2.2. Qualitative research methodology

Qualitive research methods arose from the fields of social and behavioural sciences, as a method of "study[ing] things in their natural settings, attempting to make sense of, or to interpret, phenomena in terms of the meanings people bring to them."(222) This "interpretive, naturalistic approach to the world" can provide rich and informative data across a broad range of topics. Often these topics could not be studied, or could not be

as well described, by quantitative research methods. Qualitative approaches can also be used to complement and add meaning to the numeric and statistical outcomes of quantitative methods.(223)

Ormston, Spencer, Barnard and Snape described the key elements that make up qualitative research.(166)

- The research aims and objectives should be focussed on generating a detailed, interpreted insight of participants' worlds by hearing their personal histories, experiences and perspectives, and learning about the conclusions they draw from their social and environmental circumstances.
- Data should be generated using adaptable and responsive methods that reflect the social context of the research and, in being non-standardised, can be modified to allow exploration of new and emerging issues with each participant.
- Qualitative research should yield rich and complex data that can be analysed in a way that retains subtlety and complexity, respecting each participant's individuality, as well as identifying recurrent, overarching themes.
- By retaining an open attitude to themes and theories as they evolve during analysis and interpretation, the research output will be a detailed description of the topic under study, embedded in participants' perspectives.
- The investigator's role in the research process should be explicitly acknowledged, using a reflexive approach. In some cases, this requires researchers to report their individual experiences and viewpoints on the topic in question.

2.3. Methods

2.3.1. Study design

Qualitative methods were judged to be the optimal research approach for this study, as they would provide a detailed picture of participants' and their relatives' experiences of living with MPM and participating in the TILT trial.

One to one interviews and focus groups were considered as potential methods of collecting qualitative data. Both have advantages and disadvantages, with interviews offering the opportunity to discuss individual experiences and personal matters to a deep level, whilst focus groups tend to yield a wider range of experiences but with less depth of discussion.(224) One to one interviews were chosen for participants following discussion with the PPI group who provided their views about potential data collection methods. Men with MPM stated, universally, that they would be reticent to share their experiences in a group setting. In contrast, focus groups were originally planned for relatives as it was thought that group sessions would encourage free discussion, with the opportunity for people to share or contrast their experiences, generating richer data.(225) Additionally, it was felt that the reduced intensity of a group setting may encourage relatives to speak more openly, particularly about any perceived negatives or criticisms of the trial, a feeling that was supported by relatives in the PPI groups. Unfortunately, the small number of people recruited to TILT and the geographical and temporal distances between them rendered focus groups unfeasible, and so one to one interviews were ultimately also performed with relatives.

2.3.2. Aim

The aim of the qualitative interviews was to explore the experiences of participants and their relatives of living with MPM and participating the TILT trial and to assess the acceptability of research processes. The qualitative research aimed to answer the question "Was TILT acceptable to participants and their relatives?"

2.3.3. Participant eligibility

Because the aim of the qualitative study was to explore experiences of trial participation, all TILT participants were eligible. Participants' relatives were also invited to participate because previous qualitative research has highlighted that people with MPM often display stoicism in response to their condition,(174) and because PPI groups suggested that relatives and carers would have had different experiences and perspectives on the trial. On the suggestion of PPI members, friends, carers and other acquaintances were also included as potential participants, provided the TILT participant agreed to their involvement.

An eligibility criterion for TILT was that people should have a predicted life expectancy of at least 12 weeks, therefore it was not expected that many participants would die before qualitative interviews could take place. However, previous clinical trials in this patient population have shown that clinicians are poor at predicting survival, and therefore it was acknowledged that some participants may not survive long enough to take part in the qualitative study.(40) Bereaved relatives' perspectives on research were likely to be unique. It may be that having a relative participate in research during the

terminal stages of their life placed an unacceptable additional burden on their loved one's limited energy or consumed too much of their remaining time together. Contrastingly it may have provided a sense of purpose during a person's final days and the opportunity to leave a 'legacy' through participating in research. A critical interpretive synthesis of 239 quantitative and qualitative research studies examining research participation at the end of life commented on these possibilities, and ultimately concluded that the majority of participants' experiences in end of life research were positive, as long as the research approach was sensitive to their needs.(226) I were keen to understand the experience of research at the end of life in people with MPM, hence the option to interview bereaved relatives was included in the study protocol.

2.3.4. Participant sampling

Sampling for qualitative interviews can take several forms, and different strategies may be used in combination. Methods include convenience sampling, purposive sampling, theoretical sampling and snowball sampling.(227) Convenience sampling, in which participants are identified opportunistically, is often driven by timing or resource limitations. It can be helpful in recruiting difficult to reach groups and may be associated with low research costs, but often results in low credibility data with limited transferability. In contrast, purposive sampling involves deliberate selection of certain individuals to participate, based on specific characteristics or experiences. Purposive sampling can be employed to ensure a broad selection of participants is enrolled, to give the most rich and varied perspective on the topic being studied. To do this, the

researcher needs to identify the characteristics of interest, based on their own experience of the research area and supporting information from the existing literature. Another approach, theoretical sampling, is a dynamic strategy in which participants are selected to test emerging theories that have arisen from analysis of data from previous participants. It has similarities to purposive sampling as there is a purposeful element to it, however, it is undertaken alongside data analysis and is directly informed by findings in the data. Finally, snowball sampling is a technique of expanding the study population by asking an existing participant to suggest other people who would be willing to participate. This approach can be used to augment populations sampled via other methods and is useful for recruiting from close-knit or hard to reach communities.(227)

In this study, purposive sampling was planned, with the aim of enrolling participants who had experienced each aspect of the trial, i.e. control participants, participants who received BCG or OK432 and people who declined any element of the trial. Due to the small numbers recruited to TILT, this amounted to approaching all TILT participants and inviting them to take part in the qualitative study. Recruitment of relatives was similarly purposive, with additional snowballing to extend sampling to the wider community of family and friends.

2.3.5. Sample size

Sample size in qualitative studies is often determined by saturation, the point at which no new concepts or themes are detected in the data.(228) However, predicting the number of interviews needed to achieve theme saturation can be difficult, especially if

the study is researching a novel or unfamiliar area. Certain factors are associated with reaching thematic saturation after fewer interviews, for example if a homogeneous group is interviewed about a similar experience or with a narrow objective.(229)

The concept of saturation arose out of Grounded Theory, based on a constant comparison approach to analysing qualitative data.(230) With constant comparison, each new observation or interview is analysed and compared with the pre-existing analysis to assess for similarities and differences. Using this approach, the point of theme saturation is relatively easy to identify as no novel data or themes are found in successive interviews. However, saturation can be less easy to identify using other qualitative analysis methods and, as a result, saturation is often claimed by researchers without a clear explanation of how it was assessed or understood outside of the Grounded Theory approach.

An alternative model for determining sample size is the concept of information power.(231) Proposed by Kirsti Malterud and colleagues in 2015, information power describes the amount of information relative to the study that a particular sample holds. Information power is influenced by the aim of the study (i.e. whether a narrow or broad subject is under investigation), the specificity of participants (i.e. whether they share certain characteristics or experiences), the quality of the dialogue, whether the analysis is case-based or cross-case and whether new theories are being generated. Good quality dialogue, exploring a narrow topic with a specific group of participants, analysed case-

based using an existing theoretical model will have high information power and require the fewest participants.

The sample size for the TILT qualitative study was initially based on achieving theme saturation, however, this approach was reviewed following publication of Malterud's concept of information power. Fortunately, there were similarities between the two approaches in that both suggested a relatively modest number of participants would be acceptable. Specifically, the TILT population was relatively homogeneous/ specific (predominantly White British men, aged between 60 and 80, with a background in industrial occupations) and they were interviewed about a narrow and shared experience (living with MPM and participating in TILT). Correspondingly, their relatives were all White British women of retirement age, who had lived through the similar experience of caring for men with MPM during the trial. Interviews were analysed across cases, but the intention was not to develop new theories. Therefore, information power was expected to be high and a small number of interviews (i.e. the majority of the seven TILT participants and a similar number of relatives) would be sufficient to achieve the study aim.

2.3.6. Participant invitation

Participants were invited to take part in the qualitative study in person, following completion of their final TILT trial assessment visit. If they were interested, they were provided with a PIS. Participants' relatives were also approached at the final trial visit if

they had attended with the participant or, if they had not, via a letter with the PIS enclosed, given to the TILT participant to take home.

Bereaved relatives were sent a letter 6 weeks after the TILT participant's death, which offered condolence and thanked them for their relative's participation in the trial. The letter included a brief description of the qualitative study, a PIS and an opt-in form (with stamped addressed envelope) to be returned to the study team if the person was willing to be contacted to discuss the study further (Appendix 5). The letter stated that if the study team did not receive a reply, no further attempts to contact the person would be made. The letter was reviewed and approved by the trial PPI group, to minimise the risk of causing distress. If a bereaved relative returned the expression of interest form, they were contacted by telephone by a member of the trial team.

Potential participants were given sufficient time to read the PIS, usually at least 72 hours. After this period, a member of the trial team contacted them by telephone to discuss the research and answer any questions they may have. At the end of the conversation, people were asked whether they were willing to participate. If they agreed, a time and date was agreed and participants were asked where they wished the interview to take place. I anticipated that participants would feel more comfortable in their own homes and would be more likely to talk openly in that setting. Additionally, since I was going to perform the interviews, as a hospital doctor who had had previous clinical interactions with participants in the hospital setting, I felt that the interview dynamic would be more balanced if participants were "on home turf". Consultation

with the trial PPI group confirmed this, with the majority stating that they would prefer to have an interview in their own home. Alternative options were provided, however, including the home of a friend or relative, a neutral space e.g. village hall or library, their local hospital or a non-clinical space at a local university.

2.3.7. Interview process

I (Anna Bibby, AB) conducted the interviews myself. I am a White British female in my late 30s with qualifications of MBChB, BSc, MRCP, DTM&H. At the time of the study, I was employed part-time as a clinical academic and part-time as a consultant respiratory physician, on a background of 15 years clinical experience in the NHS. I was the Principal Investigator for TILT and, as part of my PhD programme, had received formal training in qualitative research methods, qualitative analysis and NViVo software via taught courses at the University of Bristol. I also received support and guidance in qualitative methods and social theory from Prof Rachael Gooberman-Hill (RGH), a Professor of Health and Anthropology at the University of Bristol. All participants had met me on at least one prior occasion, usually in the course of their clinical care. All were aware of my role as PI for TILT.

Where possible, interviews were held with just the participant and me present, however in three interviews participants requested their relative(s) be in attendance and this was permitted. Participants provided written informed consent for the interview, including consent to be audio-recorded, for the audio-recording to be stored electronically and for anonymised quotes to be used in the final report. English was the first language of

all participants, so all interviews were conducted in English, without translators. Interviews lasted between 24 minutes and 92 minutes. Field notes were not made.

Interviews followed a semi-structured approach using a pre-specified interview topic guide (Appendix 6), with scope for additional questions or discussion based on individual participants' responses. Participants were asked about their prior experience of clinical research, their reasons for participating (or not) in TILT and their views on TILT-related trial processes. Participants who had received an IMP were asked about their experience of IMP administration and effects. Participants who declined to participate in any element of TILT were asked about their reasons. The TwiC design was explained to participants and their opinions were solicited as to whether they felt the design was acceptable, fair and transparent. The topic guide evolved iteratively with successive interviews, with additional questions about participants' attitudes to other treatments e.g. chemotherapy added later.

The topic guide originally included exploration of participants' individual diagnostic pathways, as well as their feelings and responses on receiving the diagnosis of MPM. However, before the first interview took place, the research team became aware of an existing qualitative study that was investigating a similar topic. The RADIO-meso study (Receiving A DIagnosis Of mesothelioma), funded by Mesothelioma UK, consisted of interviews, focus groups and an electronic consultation exercise with patients, relatives and healthcare professionals.(232) Based on the qualitative findings, a set of recommendations was published to help healthcare professionals improve the

experience of being diagnosed with MPM.(233) To avoid duplication of this work, the topic guide was changed and questions relating to diagnosis were removed.

2.3.8. Data analysis

Interviews were digitally audio-recorded, with recordings subsequently transcribed verbatim and anonymised. Pseudonyms were generated for each participant and are used throughout this thesis. Transcripts were reviewed and checked for accuracy, then re-read and recordings listened to, to increase familiarity with the data. Transcripts were uploaded to QSR NVivo v12 qualitative analysis software.

Thematic analysis was selected as the method of analysis for this study. Thematic analysis is "a method for identifying, analysing and reporting patterns in data... in rich detail", whilst also enabling interpretation of certain elements of the topic.(228) Of the many diverse analytic approaches used in qualitative research, thematic analysis has been suggested as a foundation method and one of the first that researchers should learn.(228) This was one reason for selecting it for this study.

Unlike several other qualitative analysis methods, thematic analysis is not tied to a specific theoretical or epistemological position. This lends it flexibility and it can be as equally applied to a realist/ experiential paradigm as it can to more theoretical approaches.(234) Unfortunately its independence from formal anthropological or sociological theories, as well as its flexibility, have led to accusations that thematic analysis is a vague approach, in which "anything goes".(235) In fact, the processes

required to perform thematic analysis are rigorous as long as certain analytical decisions are made upfront.(228) If these decisions are explicitly stated, there will be nothing ambiguous or vague about the analysis. These key decisions are:

- Whether the aim is to provide a broad description of the whole dataset or a detailed depiction of one specific element.
- Whether the analysis will be approached in an inductive or deductive manner.
- Whether themes will be identified at a semantic or latent level.
- Whether the research is being undertaken from a realist or constructionist perspective.

For this study, a rich account of the entire dataset was desired, with a specific focus on the acceptability of the TwiC design. An inductive approach was chosen, whereby themes were directly informed by the data, with no preconceived ideas about what themes were present before analysis began. The alternative, deductive coding, entails the researcher approaching the data with list of pre-determined themes and identifying codes within the text that correspond only to the themes of interest. Both methods have their merits, with inductive coding seen as a useful approach for generating hypotheses, whilst the deductive method can be more hypothesis testing.(236) An inductive approach was deemed preferable for this study as the lack of prior qualitative research on the subject meant that there were no existing hypotheses or established themes to apply deductively to the data. Inductive coding allowed the data to determine the themes and ensured that the data was comprehensively represented, with all identified themes truly grounded in the data.

The next two decisions related to the level at which meaning was ascribed to themes and the relationship with underlying socio-cultural context. For example, a semantic theme is based on explicit information, interpreted at a surface level, whilst latent themes explore deeper to identify associated beliefs or philosophies underpinning the surface statement.(228, 237) Latent themes almost always require a degree of theorising and are usually (but not always) associated with a constructionist approach.

Constructionism is based on the theory that all experiences and meaning are socially created and are not, therefore, inherent to a particular individual.(228) Qualitative analysis undertaken with a constructionist approach is focused on understanding the socio-cultural context that informs an individual's interpretation of an experience. The alternative is a realist interpretation, which assumes a direct and usually unidirectional relationship between language and meaning, i.e. a participant's statement is an authentic representation of their experience or meaning, and it is that meaning (or experience) that is of interest for the research.

In this study, I wished to understand the reality of trial participation at an individual level, rather than aiming to appreciate the deeper socio-cultural motivations informing participants' experiences or to formulate a theory of trial participation in people with MPM. Hence, I chose to adopt a realist, semantic approach.

Whilst learning about inductive approaches to qualitative research, I read about Glaser and Strauss' Grounded Theory.(230) This is a specific inductive method, where researchers attempt to enter into the research field with an entirely open mind to allow theory to be developed inductively from the data. I considered whether Grounded Theory was appropriate for this study, however, given the research team's history of clinical and academic work in the field of MPM, I ultimately felt it was unsuitable, as a truly naïve approach was not possible. Instead I elected to use a general inductive approach, as described by David Thomas in 2003.(238) This approach afforded a degree of flexibility by acknowledging that the analysis would be shaped by both the overall aim of the research (determined deductively) and the interpretation of the raw data (analysed inductively). Thus, it was anticipated that the qualitative study would produce several novel, inductively-generated themes, embedded within two overarching concepts determined by the study objectives, i.e. the experience of living with MPM and the experience of participating in the trial.

Qualitative data can be organised for analysis using the Framework Method, in which themes are indexed using a structured matrix.(239) This can be used for deductive coding, where the matrix is pre-populated with specific themes and topics of interest, or completed inductively with themes identified during, rather than prior to, analysis. During coding, the matrix is filled in with sections of transcript representing each theme, hence the framework is applied to the data. Whilst this is a neat way to structure codes, a potential pitfall of the framework approach is that it organises data in a manner that is deceptively similar to a quantitative spreadsheet. This may tempt novice qualitative

researchers to apply quantitative descriptions to the data, e.g. “Eight out of ten participants commented on X theme”.(239) This would be an incorrect interpretation of the approach that would miss almost all of the richness that is integral to qualitative analysis and the data it based on. For this thesis, the flexibility offered by Braun and Clarke’s method of thematic analysis and the opportunity it provided to produce a detailed and complex account of what was expected to be a rich dataset was more appealing. Deciding key elements of the analysis at the outset (i.e. inductive interpretation based on a semantic and realist approach, aiming to provide a broad description of the whole dataset) ensured that the thematic analysis would be rigorous and would yield insightful and trustworthy results.

For these reasons, thematic analysis was performed in accordance with the six-step process described by Braun and Clarke, consisting of:

1. data familiarisation,
2. creation of initial codes,
3. searching for themes,
4. review of themes,
5. definition and description of themes, and
6. publication of data.(228)

Having conducted all the interviews and transcribed several, I was immersed in the data from the outset. Transcripts were inductively coded to develop an initial code list. Interviews were coded sequentially, with the code list reviewed prior to each successive interview. A subset of four interviews was independently double coded by RGH. Code-

lists were compared and refined, based on discussion between RGH and me. I then coded the rest of the data and grouped coded segments into categories and themes. Themes were mapped graphically to identify connections between themes and to develop a descriptive account of the whole dataset.

2.3.9. Ethical considerations

Participation in the qualitative study was voluntary and participants were given as much time as they required to consider their decision to participate. Participants were assured, in writing in the PIS and in person at the start of the interview, that they could withdraw at any point without affecting their future clinical care. All participants provided written informed consent prior to participating, including consent for the interview to be digitally audio-recorded and stored, and for the use of anonymised quotations in the final report. Participants were informed that the content of the interview was confidential and would be anonymised during transcription. All data was stored in accordance with the Data Protection Act.

It was recognised that participants would either be personally living with or caring for someone with terminal cancer and that reflecting on this experience could potentially cause distress. This was explicitly recognised in the PIS and participants were offered a list of people they could contact after the interview if they wanted additional support. A standard operating procedure was produced for responding to distress in qualitative interviews and any participants who did become distressed were offered the contact details of a self-referral NHS psychology service.

The research team acknowledged that there were specific ethical issues around approaching bereaved relatives to participate in the qualitative study. However, I felt it was important that these people had the opportunity to share their experiences of caring for someone who was participating in research during the end of their life, as these experiences may have differed quite significantly from other participants'. Similarly, I did not want to deprive deceased participants of the chance to have their stories heard. Equally, however, I did not want bereaved relatives to feel pressurised to take part nor did I wish to intrude upon their grief. I discussed the subject extensively with members of the PPI group and with attendees at several local mesothelioma support groups (both of which included people whose partners had died from MPM). Following these conversations, we decided that it was appropriate to approach bereaved relatives on a single occasion, via letter, with an opt-in offer to participate in the qualitative study. A specific PIS was written for bereaved relatives. Both the invitation letter and the PIS were reviewed on two occasions by the PPI group to minimise the chance of causing distress. All documents were reviewed and approved by the Research Ethics Committee before the study began (ref 17/SW/0080).

2.3.10. Reflexivity

When designing any research study, it is important to identify potential factors that may influence the findings and strive to minimise them wherever possible. However, clinical research cannot and does not occur in a vacuum, especially in qualitative research where the researcher is inextricably embedded in data collection, analysis and

presentation. Despite all attempts to remain neutral, it is, in reality, impossible for researchers to separate themselves completely from their existing knowledge or views on a topic. It is important, therefore, to appreciate the potential impact the researcher may have had on the findings of this study. A biography has been provided in Section 5.3.7 to enable the reader to make their own assessment of how my characteristics and background may have influenced the research process and to what degree. Further discussion follows in this section.

The overall aim of the thesis was inescapably linked to my clinical experience in the field of MPM and recognition of the lack of treatment options available. My familiarity with the field may have facilitated some aspects of the qualitative study as participants did not need to explain medical terms or processes to me. My knowledge of MPM and clinical experience in this field also enabled me to establish a good dialogue about all aspects of this condition. Finally, having worked with people with advanced cancer and their relatives for several years, I am skilled in communicating about difficult topics such as incurable conditions and end of life matters.

However, my background as clinician may have been disadvantageous in other ways. Specifically, it has been suggested that healthcare professionals should not interview their own patients, as there is a chance that participants will try and please them by saying what they think the clinician wants to hear.(240) However, in situations where this cannot be avoided (such as this thesis), patients should be encouraged to speak openly, without censure or judgement. This was the approach that I used. Wherever

possible, interviews were conducted in patients' homes rather than on hospital premises to redress the dynamic of clinician and patient. Specifically I wanted participants to feel relaxed and comfortable and in control, and thought this would be more likely in familiar surroundings rather than in a sterile, clinical setting, where the doctor is usually the person in a relative position of power. To further reduce the doctor-patient dynamic, I wore professional but non-clinical clothing, with no hospital identification, stethoscope or other medical accessories. Occasionally, participants asked a clinical question during the interview and, if possible, I politely told them that I would be happy to answer the question at the end but would prefer to continue to hear about their experiences first.

The fact that I was PI for TILT may have influenced how participants related their experiences of trial participation. However, it was clearly stated at the beginning of each interview that the aim of the process was to learn from their experiences and to improve research for future participants, so participants should not be afraid to express their views. I tried to be humble and receptive, and to respond neutrally to all comments regarding the trial, whether positive or negative. Suggestions for improvement to the trial were invited and openly explored. This approach seemed to be successful, as participants appeared willing to speak freely about their experiences in the trial, including quite strong opinions and appropriate criticism of certain areas of the trial in the case of one participant and his wife.

2.4. Results

2.4.1. Participant characteristics

Eleven interviews were performed with five of the seven (71.4%) TILT participants and seven of nine (77.8%) relatives approached, two of whom were interviewed together (Ida and Janet). Ida was also present for her husband Harry's interview, and Bob was present for his wife, Eleanor's interview. Aside from Ida and Bob, participants were interviewed on one occasion only.

One TILT participant agreed to be interviewed but was sadly admitted to hospital and died before the interview took place. Her husband (the only relative to be bereaved during the study) did not respond to the qualitative interview invitation. The other TILT participant who declined the qualitative study was approaching the end of his life and felt too unwell to be interviewed. His daughter-in-law was interviewed.

Participant characteristics are shown in Table 5.1. Interviewees had participated in both the active intervention arm and the control arm of TILT. Unfortunately, the sole TILT participant to receive OK432, and coincidentally the only female participant in the trial, was one of the people who did not complete a qualitative interview. Therefore, the qualitative interviews reflected the experiences of men who received BCG or were controls. Interviews were completed with the TILT participant who declined to receive BCG having been offered it, and with the relative of the control participant who declined further follow up.

Study ID	Pseudonym	Role	Sex	Age	Study site	Interview location
32-6T	Alan	TILT participant (BCG)	M	71	Bristol	Patient's home
33-9C	Bob	TILT participant (Control)	M	84	Oxford	Patient's home
32-6T-W	Caroline	Wife of Alan	F	71	Bristol	Patient's home
104-1T	Dave	TILT participant (BCG)	M	61	Taunton	Community Hospital
33-9C-W	Eleanor	Wife of Bob	F	81	Oxford	Patient's home
32-24C	Frank	TILT participant (Control)	M	81	Bristol	Patient's home
32-24C-W	Georgina	Wife of Frank	F	79	Bristol	Patient's home
32-27T	Harry	TILT participant (Declined BCG)	M	74	Bristol	Patient's home
32-27-W	Ida	Wife of Harry	F	72	Bristol	Patient's home
32-27-D	Janet	Daughter of Harry	F	48	Bristol	Patient's home
32-38C-D	Kate	Daughter-in-law of control participant	F	43	Bristol	Community Hospital

Table 5-1 Characteristics of participants in the qualitative study

2.4.2. Themes

In keeping with the overall aim of the study, the majority of interview content related to two overarching topics: the experience of MPM and the experience of research participation. Within these topics, seven themes were identified:

i. physicality,

ii. quality of life,

iii. uncertainty and risk,

iv. anxiety and the future,

v. motivations for participating in research,

vi. downsides of research participation, and

vii. specific TwiC features.

The first three themes were common to both overarching research topics, indicating a commonality of experience that spanned having MPM and participating in research. In contrast, theme iv appeared to relate only to the experience of having MPM, whilst themes v, vi and vii were predominantly grounded in the experience of the trial. The quality of life theme (theme iii) was linked with participants' motivations for participating in the trial (theme v), whilst the theme about uncertainty and risk (theme iii) informed some of the reported downsides of trial participation (theme vi). Each theme consisted of three or four sub-themes, which are listed in Table 5.2. The relationship between the seven themes, their sub-themes and the overarching research topics is illustrated in Figure 5.1.

The same themes arose from interviews with trial participants and interviews with their relatives. Interestingly, however, perspectives often differed between the two groups. Figure 5.2 shows examples of themes that were shared between participants and relatives where the experience of the theme varied and others where they accorded.

The remainder of this chapter consists of a description of each theme, with an account of the associated sub-themes. For each theme, the relationship to the overarching

research topics are outlined and areas where participants' and relatives' positions diverged are highlighted. All names are pseudonyms.

Major theme	Subtheme
Physicality	Impact of symptoms Stoicism and valuing strength Relatives as advocates Experiencing side effects
Quality of life	Quality not quantity Decision-making: chemotherapy Decision-making: clinical trials
Uncertainty and risk	Gathering information and seeking certainty Appreciating equipoise Perception of risk Commitment to decisions
Anxiety and the future	A terminal diagnosis Impact on relatives Grieving for lost opportunities Keeping positive *vs* giving up
Motivations for participating in research	Altruism Reciprocity Understanding the science Relatives' reluctance
Downsides of research participation	Timings Organisation Communication Completing trial paperwork
Specific TwiC features	Lack of placebo Blinding of controls Attrition

Table 5-2 Themes describing the experience of MPM and participating in a clinical trial

Figure 5.1 Schematic representation of themes, sub-themes and their relationship to each other and to the overarching research aims

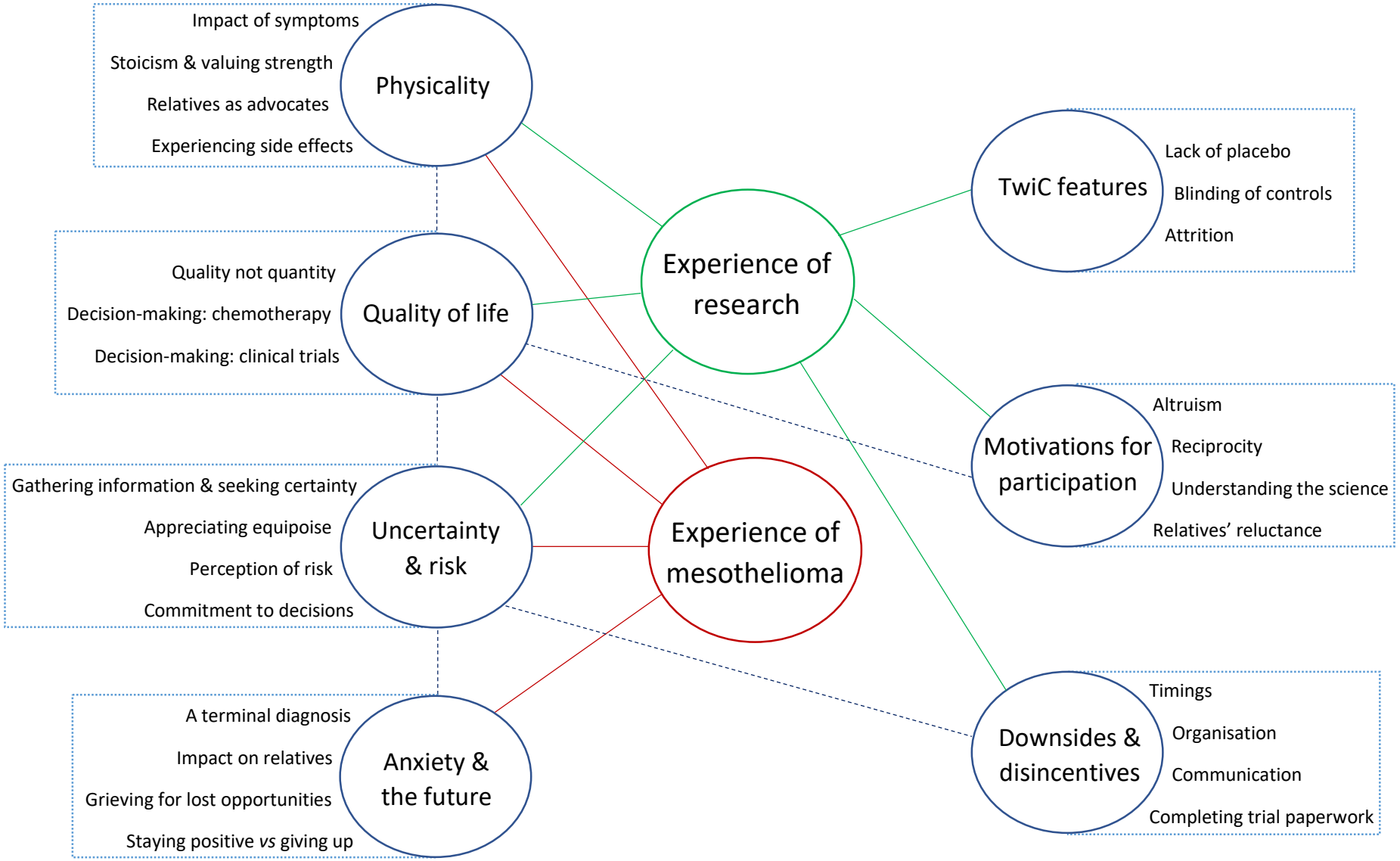
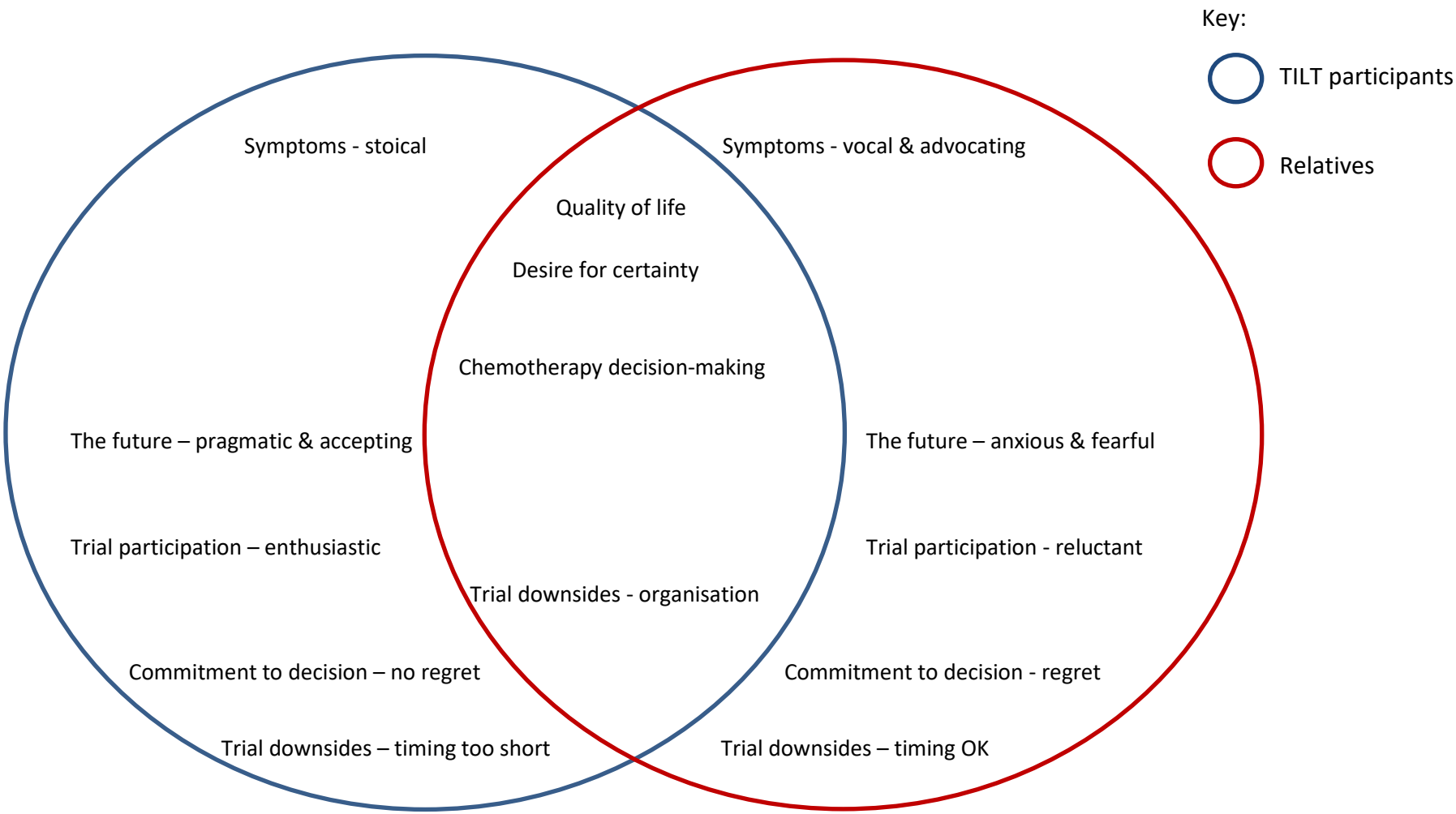


Figure 5.2 . Examples of themes where participants' perspectives and their relatives' agreed and differed



2.4.2.1. Physicality

2.4.2.1.1. Impact of symptoms

Almost all participants commented on the physical aspects of MPM, frequently mentioning symptoms of breathlessness and fatigue. Symptoms often impacted on people's day-to-day activities and, for some participants, elicited strong emotions, including frustration and anger.

> *"I've only got to walk up the top of the garden and I can feel it and I'm struggling to breathe." Harry, 74 M, person with MPM.*

> *"Just the sheer physical effort of talking to somebody, and you know how he loves to talk, and that really cost him. If he did anything physical, he'd spend three or four days recovering from the smallest thing, and for [husband] he just hated it, every second of it." Caroline, 71 F, wife of person with MPM.*

2.4.2.1.2. Stoicism & valuing physical strength

Despite being limited by their symptoms, men with MPM often underplayed their physical problems.

> *"I know I've got it … but I don't feel bad. I'm okay, I like to walk, my body still allows me to walk and I do it." Bob, 84 M, person with MPM.*

"Larry done a lot of, 'Oh, I am fine, I am great, I am OK,'" Kate, 43 F, daughter-in-law of person with MPM.

One possible reason why patients underplayed their symptoms was that men with MPM appeared to place a high value on physical health and strength, often emphasising their previous high levels of fitness.

"I have always been fit and healthy." Dave, 61 M, person with MPM.

"I remember he came out on the bottom floor and said, 'Would you like to come up to my office by lift or do you want to walk up?' and I said I would walk up, so I walked up five flights of stairs." Frank, 81 M, person with MPM.

"I can remember on the Wednesday a friend came round wanting the concrete mixer, and I was humping and carrying, and I felt absolutely wonderful, I felt fine. And that's the last time I felt really, you know, a mountain isn't a problem." Alan, 71 M, person with MPM.

In response to this, several people with MPM acknowledged that their physical strength was deteriorating, and that they were having to realign their expectations with their ability. For most, this was difficult to come to terms with, and they often expressed sadness and regret at their new reality.

"It really has been a hard lesson and a shock for me to have to realise that I'm going to have to give up my golf and table tennis." Frank, 81 M, person with MPM

"OK I didn't really appreciate [Nurse] saying, "You were a fit 70-year-old, now you're an unfit 70-year-old". It happened, what, over four months? I certainly wasn't ready for that. OK, she's probably right, but I wasn't very happy with that." Alan, 71 M, person with MPM.

2.4.2.1.3. Relatives as advocates

Relatives found it hard to watch their loved ones struggle with symptoms. They described feeling powerless to help, able only to watch as their husband's struggled or visibly deteriorated.

"Interviewer: Had you seen him finding things harder?

Ida: I have, yeah, especially 'cause he loved his garden and veg. It's pitiful to see him absolutely gasping for breath, isn't it?

Janet: And hard for you when you can't make it better.

Ida: Can't help him, no, that's right, yeah. You can't fix it, you can't make it easier, you just have to watch.

Janet: Yeah."

Ida, 72 F, and Janet 48 F, wife and daughter of person with MPM.

"I'm watching my husband going downhill." Caroline, 71 F, wife of person with MPM.

In response to this, several relatives had assumed the role of advocate, speaking out when their loved ones would not and campaigning to ensure their partners received the best care. Sometime these efforts were hindered by their relatives' stoicism, causing frustration. One person was particularly concerned that her relative was missing out on community palliative care input because he was not forthcoming about his symptoms.

"I was told you can't have a nurse specialist because [Larry]'s gone, 'Oh, I am fine, I am fine,' and I go, 'You actually have to tell her you are breathless! You need this, I am not doing it all'." Kate, 43 F, daughter-in-law of person with MPM.

2.4.2.1.4. Side effects

Most participants who received the investigational medicinal product experienced side effects from the trial drug. They described how this felt.

"By 9 o'clock I was running a temperature, I had flu symptoms. So I went to bed. Didn't think anything more of it, because I was expecting to get, well I was prepared. It was a little bit quicker than I was expecting to get flu-like symptoms, I thought you said, 'Within the next day or so'… So yes, we, I went to bed… Woke up, couldn't get up, I was feeling really, really, very ill. I

couldn't breathe, I couldn't do anything else… My chest was very restricted, I was basically panting." Alan, 71 M, person with MPM.

"Yeah, you know, you said, you might feel a bit unwell and all this. I felt bad. You know, I… for a couple of days I was just in bed and didn't bother getting up. I thought, I have got no mojo, not that I didn't have any strength, I just didn't have any mojo and I think that I wasn't expecting." Dave, 61 M, person with MPM.

Despite being warned about potential side effects, it seemed that participants had not expected to feel the way they did, as quickly as they did. However, for one participant, the side effects were manageable because he recognised that they were caused by the trial medication, and thought that they meant the drug was working:

"Because I had felt… well, not so well, but okay previous to it. I thought well that must be the effect of the drug… this might be doing some good." Dave, 61 M, person with MPM.

Again, the partners of men with MPM expressed how upsetting and frightening it was to watch their husbands feeling unwell. A sense of powerlessness contributed to their distress.

"It was that chain of events that happened, and I felt so helpless, [husband] thought he was going to die and to be honest I think the ambulance people did too." Caroline, 71 F, wife of person with MPM.

The same person described advocating on her husband's behalf when he was admitted to hospital. She was fiercely protective of him and fought to ensure her husband received the best possible care once he arrived in hospital.

"I just couldn't, couldn't get my head… What nurse puts a man who is going grey with blue lips, in a chair to wait for a bed? Can they not just put him on a trolley if nothing else? He's sat there and he's swaying. Can you not find him something more comfortable? I know I was rude that day, I fully appreciate it but it wasn't a good experience, and yes it was me that took up the cudgels, but again [husband] was too poorly to want to do anything about it." Caroline, 71 F, wife of person with MPM.

Clearly the side effects of the trial drug had significant physical and emotional impact on participants who received it, as well as their relatives. Interestingly, participants in the control arm of the trial also had an appreciation of potential side effects, with several people expressing relief that they or their husband had not received the trial drug.

"I'd hate to think what it would have been like if I had had the bacteria." Frank, 81 M, person with MPM.

"So, I was glad in a way that he did have the placebo because who knows what would have kicked off." Georgina, 79 F, wife of person with MPM.

2.4.2.1.5. Synopsis

The importance placed by people with MPM on good health and physical strength, and the negative impact of symptoms and medication side effects, revealed the particular values and priorities held by this patient group. These values informed their overall quality of life and shaped some of the decisions they made regarding treatment and research participation, as identified in the second major theme.

2.4.2.2. Quality of life

2.4.2.2.1. Quality not quantity

Quality of life was important to participants and their relatives, especially in light of the limited life expectancy associated with MPM.

"I think, for us at the moment, quality of life is the first priority. For the years that we have got left, and hopefully there will be quite a few, that we appreciate the quality of life." Eleanor, 81 F, wife of person with MPM.

Participants were able to balance the overall amount of time they had remaining with the importance of feeling well in that time. For most, living longer was not desirable unless it was accompanied by good quality of life.

"If I have got some extra time that's brilliant, but I couldn't face it like this."

Frank, 81 M, person with MPM.

At the time of interviewing, most participants were content with their existing quality of life and hoped their circumstances would remain similar in the future. However, this aspiration was overshadowed by an awareness that the prognosis was uncertain and that their condition was liable to change at some point.

"Long may the situation reign that I've got, but I can't bank on it, can I?"

Bob, 84 M, person with MPM.

"Janet: [We're] just happy to keep going.

Ida: Yeah, as long as he's like this, like he is, yeah.

Janet: With the new drain.

Harry: Yeah, I'm happy to carry on like this, if I could stay like it."

Janet 48 F, and Ida, 72 F, daughter and wife of Harry, 74 M, person with MPM.

2.4.2.2.2. Decision-making: chemotherapy

The desire to preserve quality of life influenced participants' decisions about chemotherapy. Most participants believed that the limited benefits of chemotherapy did not outweigh the risk of side effects. Participants were well informed about the

specific survival benefit associated with chemotherapy and were not willing to sacrifice their overall wellbeing for two to three months of longer life.

> *"No, he said as well, 'If it was only going to give me two months extra, I wouldn't have treatment, because the impact of having the treatment would affect the quality of life I was having, potentially.'" Kate, 43 F, daughter-in-law of person with MPM.*

> *"We'd seen the results of chemo and it didn't work, it was absolutely hell to go through, so there didn't seem any point; if you're not going to get more than a couple of months out of it, what is the point? That was the decision that was reached." Caroline, 71 F, wife of person with MPM.*

> *"We had this long discussion about should he have the chemo or not and we were both of the opinion that he shouldn't have it… He looked at it from a much more practical side, went into all the statistics and found out how short a time it would prolong his life and thought, 'Well, on balance it's not worth it'." Georgina, 79 F, wife of person with MPM.*

One participant was particularly eloquent in summarising what he perceived to be the net gain from chemotherapy:

"I don't see much point in bashing yourself with a hammer just to feel better when it stops." Alan, 71 M, person with MPM.

Relatives were supportive of their husbands' decision not to receive chemotherapy. In some cases, relatives recognised that their family members were too unwell to tolerate chemotherapy and appeared relieved that it had not been offered to them. As with the previous theme, relatives were protective of their family members and keen to ensure that everything was done in their best interests.

I had already said to him the day before we went in, 'He won't be offered any chemo', he wouldn't have sustained it, you know, because you get obviously very unwell with chemotherapy, you have to have a reserve, he didn't have any reserve." Kate, 43 F, daughter-in-law of person with MPM.

"At the time he was looking ill, so it was like I could understand why the chemo wouldn't be suitable for him." Janet, 48 F, daughter of person with MPM.

2.4.2.2.3. Decision-making: clinical trials

A similar pattern emerged when participants described the decision whether to participate in clinical trials. People with MPM were well-informed and able to evaluate the potential benefits of receiving a trial medication against the possible impact of side effects on their quality of life.

"[Doctor] sent me a recent paper, which he was very positive about. But when I looked at it, it talked about dramatic improvements, doubling of life expectancy from six months to twelve months type of thing, so I thought, mmm, umm, and with some really serious side effects, and so I decided that wasn't for me because quality of life is important." Frank, 81 M, person with MPM.

Concern about side effects from trial medication was the predominant factor in one participant declining to receive BCG in TILT.

"That first [trial], what I, what I backed out of… I thought, well, with all my ailments another one ain't gonna be very nice, so that's the reason why." Harry, 74 M, person with MPM.

His wife had harboured similar concerns about TILT and expressed a sense of relief when her husband chose not to participate in the trial.

"I knew that [husband] would probably say he would help in any way, but when you mentioned this… that putting bugs into him? And he'll be feeling like he's got the flu for a while and I thought, 'Oh, I don't know, he's getting better, he don't need any of that'. That did play on my mind. But he said he's not gonna, he wouldn't do that... I was, yeah, I was relieved." Ida, 72 F, wife of person with MPM.

2.4.2.2.4. Synopsis

People with MPM tended to make rational and pragmatic decisions, with quality of life at the forefront of their decision-making. Participants sought out information to enable them to balance potential benefits e.g. of treatment, against the perceived detriment to their quality of life. Whilst this approach helped people make informed decisions, it required objective data, creating a desire for certainty that could not always be fulfilled, as described in the next theme.

2.4.2.3. Uncertainty

2.4.2.3.1. Gathering information & seeking certainty

People with MPM were knowledgeable and actively sought out information to help them make decisions and plan for the future. They often showed a preference for factual, numerical data.

> *"A statistic I used to have at the back of my head for meso is that – I'll just get this right – five per cent of people live for five years and that's the sort of figure, that's the statistic I want." Frank, 81 M, person with MPM.*

> *"I mean reading various leaflets and [wife] going on the internet and kids doing various stuff, [son] particularly. [They're] quite convinced that I've only got two and a half years to live." Alan, 71 M, person with MPM.*

The search for information was often driven by family members, who consulted a wide range of sources. Many people accessed the internet, others approached acquaintances with scientific backgrounds or their GP. One person discussed things with another MPM patient when deciding whether to have an IPC inserted.

"Then the missus was on Google." Dave, 61 M, person with MPM.

"We, well [wife], wanted some additional information, so we went to see our local GP." Alan, 71 M, person with MPM.

So, then we talked about it, and [son] went through to his friends in [Drug Company], came back and said, 'There really isn't much they can do, but there are several treatments that have possibilities. But Mum, you have to understand, it's not going to stop it.'" Caroline, 71 F, wife of person with MPM.

"Before I had the IPC, there were a couple of questions that I wanted to ask and I asked [Nurse], 'Once it's settled down, can you lie on it? And she said, 'I don't know. But I know a man who does.' So she gave me [patient]'s name, and [he] phoned me about 4 or 5 hours later and explained the situation. Which was nice." Alan, 71 M, person with MPM.

In gathering information, participants wanted certainty and found uncertainty difficult to handle. Participants wanted information to be unequivocal and expressed frustration if the information they were given was ambiguous or not specific to them.

> *"You know, one person says, 'It is not going to really do you a lot of good'. Another person says, 'Well, we don't know, it might do'. So, what do I do? I would rather somebody say, 'It is of no use to you whatsoever and don't bother' or, 'Go for it'. But don't wishy-washy in between either a yes or a no."*
> *Dave, 61 M, person with MPM.*

> *"[Doctor] said the other day, 'I can't give you an answer to that'. 'Why not?' I said, 'You keep telling me that there are certain key things that are similar to all meso patients, therefore you should be able to give me an answer to that question'. 'Yes, but it's always different in different people…' 'That I fully accept, but why can't you tell us what is common to all meso patients, apart from the fact that they're not going to get better?' 'Well, because…' 'No, don't prevaricate, I don't want that and [husband] doesn't need that'.*
> *Caroline, 71 F, wife of person with MPM.*

2.4.2.3.2. Appreciating equipoise

Participants expressed confidence in their clinicians' knowledge (*"I am looking at you as being an expert in the field" Dave, 61 M, person with MPM*). However, the corollary of

this was a perception that clinicians should be omniscient, even to the extent of being able to predict the future.

Alan *"I didn't have the anaphylactic shock, so what was it that I had? And nobody seemed to know. It was a reaction. It was a severe reaction, but I remember [Doctor] saying we didn't think it was going to be so severe.*

Interviewer *No*

Alan *But that's what he's there for."*

Alan, 71 M, person with MPM.

This had implications on participants' understanding of trial equipoise. During some interviews, participants revealed that they had assumed clinicians had prior knowledge about the efficacy and overall effects of the trial drug, not realising that this lack of knowledge was the very reason the trial was being performed.

"I felt at that time you wouldn't have offered him something that would have fundamentally made him a lot worse." Caroline, 71 F, wife of person with MPM.

"I accept you don't know how I am going to react to something [but] It would also be nice to say, 'OK, you'll probably take 3-6 months to get over this.'" Alan, 71 M, person with MPM.

2.4.2.3.3. Perception of risk

The sense that clinicians had a greater knowledge of the trial drug than they were sharing impacted on participants' perceptions of the risks involved in the trial. All participants who received a trial drug were provided with comprehensive verbal and written descriptions of the potential adverse effects, including numeric estimates of the likelihood of each side effect and depictions of possible severity. Despite this, both participants who experienced a reaction professed surprise that it had occurred.

> *"Yeah. I didn't realise at the time, after you gave me the drug, how bad I was going to feel." Dave, 61 M, person with MPM.*

> *"There seemed to be a great deal of lacking of knowledge as to what was happening. Yes, the leaflet said, you know, 'You may feel terrible' and then went on, 'If it was this, then steroids' and various other things you can get, but… err, had anyone told me I could feel so rough?" Alan, 71 M, person with MPM.*

The desire for certainty arose again in this context. The participants and relatives of those who experienced a reaction had expected to be warned about the specific symptoms they ultimately experienced. Alongside this personal prediction, they described wanting assurances about how long the side effects would last and a guarantee that they would resolve eventually.

"If you ever said well this is going to put you in bed for a couple of days or it possibly could put you in bed for a couple of days…then I would have gone, 'Yeah, okay I can live with that'." Dave, 61 M, person with MPM.

"I think if perhaps we'd been made more aware of what those negatives could be. Maybe not [husband], but if you'd actually said to me, 'This is what he's going to experience'" Caroline, 71 F, wife of person with MPM.

"I don't think I'd have a problem if you told me I was going to feel really, really rough and that's one of the side effects. Um, hopefully you'd get over it within a month or 6 weeks. I think, but I'm not sure, that I would probably have said, 'OK.' I'm going to feel really, really rough but at least at the end of it… I would know that I was going to be over it. If I was going to get over it, you don't mind." Alan, 71 M, person with MPM.

The information provided in the PIS did not prepare people sufficiently for the reality of experiencing an adverse event. People did not seem able to relate to theoretical risks described on paper. Some participants did not read the paperwork, whilst others read it, but did not believe it would happen to them.

"No, I am interested but… yeah, I don't know. A lot of it, if it involved reading five sheets of A4, then I wouldn't have had any information because I am

not… word of mouth and I am fine, but I just can't be bothered with all this [paperwork]." Dave, 61 M, person with MPM.

"Having read leaflets that you get with your pills and the rest of it, and having read about the side effects you might get, I must admit I do get two thirds of the way through and I think, 'Really?'. I was certainly ill-prepared for having the reaction I did." Alan, 71 M, person with MPM.

One relative provided another perspective on risk perception, suggesting that for her husband, the altruism that motivated him to participate in the trial was greater than could be deterred by the risk of complications.

"I think he was aware of [the risks]. Yeah. But I think the desire to be part of some research and perhaps doing some good was stronger than his fear of having some side effects at that stage." Georgina, 79 F, wife of person with MPM.

2.4.2.3.4. Commitment to decision

Despite feeling poorly prepared for the reactions they experienced, participants did not regret their decision to participate in the trial and were confident that they would make the same choice again.

"Interviewer: *Do you think if we had been clearer… and said, 'Look, for some people this has happened, to some people this has happened', given you the worst case scenarios, would it have changed anything?*

Dave: *It wouldn't have changed it. No. It wouldn't have changed what I did… It wouldn't have changed anything."*

Dave, 61 M, person with MPM.

This commitment to a decision once it had been made reflected participants' propensity for absolute thinking and preference for certainty. It seemed that once the decision had been made, it became the "correct" decision for them, regardless of the consequences.

"Interviewer: *So, you mentioned that you didn't know you were going to be the first [participant]. Would that have changed your mind?*

Alan: *Probably not. I'd already made my decision. Right, wrong, wh*

Interviewer: *Would anything have changed your mind?*

Alan: *I don't know. Something catastrophic like, 'For God's sake do*

Interviewer: *You might reconsider?*

Alan *But I don't think so, no.*

Interviewer: *You'd pretty much decided?*

Alan *You know, I'd made the decision and I was sticking to it."*

Alan, 71 M, person with MPM.

"Make a decision, stick with it, if it goes wrong, you made it." Dave, 61 M, person with MPM.

2.4.2.3.5. Synopsis

People with MPM wanted to be knowledgeable about their condition and obtained information from a variety of sources. They preferred absolutes, sought certainty and found ambiguity difficult to accept. This impacted on the perception of trial equipoise and created challenges in communicating risks in a manner that could be assimilated and understood. It seemed likely that the desire for certainty was driven by anxiety about an uncertain future and a desire to control unpredictable events in the context of a short life-expectancy.

2.4.2.4. Anxiety and the future

2.4.2.4.1. A terminal diagnosis

The poor prognosis associated with MPM meant that the inevitable prospect of death weighed heavily on participants and their relatives. For some, the prospect of a future fatal illness had been hanging over them for some time, due to losing colleagues from the disease.

"The minute I hear MPM, I hear you have got 18 months to live… and there is no cure." Kate, 43 F, daughter-in-law of person with MPM.

"But I tend to feel when we go to [the MPM support group], every now and again somebody will say 'Oh, where's John?' 'Oh, he died'. They're almost waiting for each other to die." Eleanor, 81 F, wife of person with MPM.

"I've heard a lot, a few people, gone [i.e. died] working with asbestos and I thought, well, I'm next." Harry, 74 M, person with MPM.

Many people described feeling anxious about the future, particularly in regard to the uncertainty ahead and how to prepare for it.

"*Sometimes I sit there and dwell and think, I wonder what the actual end is going to be like. You know, am I going to be in pain, am I going to be this, am I going to be that?" Dave, 61 M, person with MPM.*

"I think it's this thing of the unknown, when you're dealing with something that is so completely outside your comfort zone in any shape or form, even from just knowledge point of view. It's hard to deal with that when you care about somebody, and you watch them deteriorating." Caroline, 71 F, wife of person with MPM.

As with the previous theme, participants often demonstrated a highly practical approach to death. Again, they seemed to want certainty and information delivered as facts and figures wherever possible.

One of the reasons I'm interested in knowing how much time I've got is how do I prepare? I mean, if it's 18 months away I'm not going to start thinking about funerals et cetera." Frank, 81 M, person with MPM.

One relative described her father-in-law learning about the average life expectancy for MPM and treating it as an absolute fact, actively counting down the time he believed he had left:

"I [know] a gentleman and he was given 6 months and he went home and put it on his calendar and then he lived his life right up to the date and then he was like [what now]?… And we talk about that, [Larry]- same thing! He said, 'Well, oh, I have got a year… well I have got eight months left now.'" Kate, 43 F, daughter-in-law of person with MPM.

The same gentleman's pragmatic attitude towards his own death manifested as macabre humour:

"He has got this Dupytren's contracture (a flexion deformity of the hand) and he said, 'Oh, that will be burnt off soon,' and I was like, 'Oh, what does that mean?' 'Well, I will be cremated!'" Kate, 43 F, daughter-in-law of person with MPM.

2.4.2.4.2. Impact on relatives

Whilst many people with MPM were matter of fact about death, their relatives were more fearful about the future.

> *"I kind of worry about the big things, like eroding ribs, bleeding out, aspiration." Kate, 43 F, daughter-in-law of person with MPM.*

Relatives were also more likely to discuss their partner's concerns, indicating that the pragmatic outlook presented by people with MPM was not always a true representation of what they were feeling.

> *"Where do you go for help? That's the thing I think [husband]'s scared about, and I'm scared about now." Caroline, 71 F, wife of person with MPM.*

Fear for their family member's health was ever present and several relatives described listening out for their relatives to check that they were still alive. The inescapable awareness of their relative's mortality permeated every minute of their lives.

> *"I used to lie awake and listen to him breathing." Caroline, 71 F, wife of person with MPM.*

> *"I then started to notice that we could hear [Larry], which was great and I said, 'That's great, I can hear him coughing, that's brilliant because I can hear if he is alive.'" Kate, 43 F, daughter-in-law of person with MPM.*

Men with MPM were aware of the impact of their diagnosis on their wives and family members. They often articulated greater concern for their relatives than they did for themselves, although were not always able to discuss their anxieties with their families.

> *"Just, um, I'm a bit worried about [wife]. Just, she won't, she just does too much and there's no way I can tell her to quiet. For example, she was insistent on coming to see me twice a day in hospital and that wasn't good. Yeah, things like that." Frank, 81 M, person with MPM.*

> *"I think [wife] is struggling a little bit. You know, she thought that, same as I did, you know, we were going to retire and live till a ripe old age of 150. But as I don't talk about it then I don't really know how she feels." Dave, 61 M, person with MPM.*

One man was particularly concerned about how his wife would manage with the practical tasks around the home after he died. He described a sense of responsibility to help her develop these skills.

> *"Yeah, it has been a big shock for [wife] because I did all the, um, how shall I put it? I did a lot of work in the house and with the shock of me having this relapse, it has been a big worry for [her] and I've been trying to work hard to get her to do a lot of things I used to do. For example, how do you check the*

tyre pressure on the tyres? How do you order oil for the central heating? I've been trying to work through it all." Frank, 81 M, person with MPM.

2.4.2.4.3. Grieving for lost opportunities

The poor prognosis associated with MPM led several people to reflect on future plans that had been spoiled and opportunities that were now lost.

"I was thinking, he is not going to be here next Christmas, like the Christmas next… (becomes tearful)". Kate, 43 F, daughter-in-law of person with MPM.

"He feels cheated now and I suppose I feel cheated too, because he's just retired and there were so many things that we hoped to go on with. Yes, we've been married for 50 years and that was very nice, but we still hadn't actually finished." Caroline, 71 F, wife of person with MPM.

However, others were more resigned to this loss and appeared more accepting of their altered circumstances.

"Bob: We haven't done any longish holidays for two years now and we probably won't.

Eleanor: Well, we've been there and done that."

Bob, 84 M, person with MPM and Eleanor, 81 F, his wife.

"Things are improving. I can walk up and down the drive. I've started driving the car just into [town] but I am realistic about it all and I wouldn't say I was depressed, I'm disappointed, but I've got to be realistic." Frank, 81 M, person with MPM.

2.4.2.4.4. Staying positive *vs* giving up

People had different strategies for coping with their altered futures, and many described trying to maintain a positive outlook on life despite the circumstances. For some people, this entailed actively avoiding negative thoughts and not allowing MPM to dominate.

"He's always had such an amazing positive attitude. He's always just refused to give in. He just keeps going and I think that's been a great help really in getting him through all these different things." Georgina, 79 F, wife of person with MPM.

"We're eating properly, we go walking, we keep active, we keep positive as far as we can and put it in the background." Eleanor 81 F, wife of person with MPM.

"I can't just sit and think about it day in day out. Otherwise, I don't know what I would do, go nuts, I think. I am not saying I put on a brave face, but it is no good dwelling on it… I don't want to sit there and think, oh, my God,

here it comes. I would rather, okay, that is symptom, I have got that. I will cope with that somehow and move onto the next one. Rather than sit and wait and think, is it coming? …I just put it to the back of my mind and don't even give it another thought." Dave, 61 M, person with MPM.

Some people actively focused on positive experiences, using techniques such as mindfulness to focus on pleasant moments during their day.

"I try to make the most of every situation. Instead of saying, 'Oh God, this is terrible having to come down here every day,' I'd try to see things and there was all sorts of nice things in the hospital. The chapel and see, the quiet rooms I found very nice as well… I came down one night and was feeling a bit down and, it would be half past eight at night, I got out of the lift and there was a gospel choir singing. I just sat down and listened, and it was so uplifting." Georgina, 79 F, wife of person with MPM.

For several participants, maintaining a positive outlook involved looking on the bright side, invoking a sense of gratitude that their situation wasn't worse.

"I think he's lucky, to be honest, there's a lot of people worse than him, so he's lucky." Ida, 72 F, wife of person with MPM.

"The [patient-reported outcome measures] were asking me to comment on situations where I wasn't feeling particularly bad. Most of the answers to the questions were either high or in the affirmative and I tended to get the feeling that I was, perhaps, a very fortunate man. I think I am." Bob, 84 M, person with MPM.

Not everyone was able to maintain a positive outlook, however, and some relatives commented that their family member appeared to have "given up". Understandably, this was upsetting and, in a poignant statement with echoes of Dylan Thomas's poem, one woman described her fear that her husband was failing to "rage against the dying of the light."(241)

"I wanted [husband] to fight it and he wasn't, and that disturbed me more than anything because I'm just not used to that… I was disappointed in that, and I think to be honest that frightened me for what was to come, because he couldn't control it, and because he couldn't control it and wasn't fighting it, I felt this is never going to happen, he's never going to fight it, and he hasn't really. He does what he can but he's not fighting it in the same way. It's almost as though he's put up a hand and said, 'Okay, this is what's going to happen, I'll let it happen now'." Caroline, 71 F, wife of person with MPM.

"[He said], 'Yes, I have gotten weak.' I said, 'So, why haven't you gone out as far as the gate and walked back again?' 'Oh, there is no point doing that, it's

a bit late now, I am too weak.' I said, 'Maybe you could go to the door and then come back again? Oh, forget it.' He said, 'Well, I am going to die anyway,' … He has kind of given up." Kate, 43 F, daughter-in-law of person with MPM.

2.4.2.4.5. Synopsis

People with MPM were acutely aware of their limited life expectancy, as were their relatives. Death was often thought about and discussed openly. Men with MPM appeared to adopt a pragmatic approach to their own mortality, whilst relatives were more likely to articulate anxiety about the future and grief for lost opportunities. Some people cultivated a positive mentality, which appeared to be a helpful coping strategy. People who were unable to stay positive, however, were perceived to have "given up", something which caused great distress to their relatives.

2.4.2.5. Motivations for participating in research

2.4.2.5.1. Altruism

People with MPM were often motivated to participate in research by altruistic sentiments and a desire to be helpful.

"The main motivator was being helpful. I can't do much, but I can help and do that." Bob, 84 M, person with MPM.

"I'd like to do anything I could to help you." Harry, 74 M, person with MPM.

There was recognition that research was necessary to progress science and medicine, especially in view of the limited options and poor prognosis associated with MPM.

> *"If it's not right for me, hopefully it'll be right for someone else. And if you don't have people with that attitude, you're never going to progress. We'll still be giving lead poisoning and whatever it is to find a cure. Bleeding, leeches and all… Without research we're still in the dark ages." Alan, 71 M, person with MPM.*

> *"There's got to be trials because otherwise you're never going to find anything that's going to help this dreadful disease." Caroline, 71 F, wife of person with MPM.*

> *"We've always been happy to help. Anything which will improve a situation… because I think it's your moral duty, isn't it, to offer what you can when you can." Eleanor 81 F, wife of person with MPM.*

2.4.2.5.2. Reciprocity

Some people were mindful of the potential ways that trial participation might benefit them, although this was rarely a primary motivational factor.

"My visits to the hospital, I know I'll get something out of it, you're gonna tell me something or teach me something or do something to make me feel better." Harry, 74 M, person with MPM.

"Of course, also, once you've decided you're going to do it, you're this focus of all this attention and all these extra things that they are taking from you that are going to be used as part of the research, but also extra things are being done to look at what's wrong with you, and that can't be bad." Bob, 84 M, person with MPM.

Most people enjoyed the regular contact with the research team that came with trial participation.

"No, I have always felt… every visit I have had, I have either seen [Nurse] or [Doctor] and they have always been chipper and upbeat, how are you and all that. Made you feel like, not something special but you know, that they want to talk to you." Dave, 61 M, person with MPM.

Participants also talked about the desire to repay the care they had received from clinicians.

"I've been looked after extremely well, given the right sort of options and a lot of guidance, and I hope I've done my bit." Bob, 84 M, person with MPM.

"I was keen to show that I appreciate what your team had been doing for me." Frank, 81 M, person with MPM.

Several participants acknowledged the reciprocal nature of the relationship.

"Well, it's a two-way process, isn't it? We want to keep [husband] around for as long as we can and you, on the other side, want to know as much as you can about the condition so that you can improve your side of it. It works both ways." Eleanor 81 F, wife of person with MPM.

"Yes, you get added value, you do. It was a mutually beneficial arrangement." Bob, 84 M, person with MPM.

For some people, the option of participating in a trial offered hope and gave people something to focus on.

"I personally think you need something to work towards, even if it's a small goal, you need that to work towards and I think that's what the trials give people. It's the combination of working towards it with the glimmer of hope at the end, that whilst you know you're terminal, the terminally of it could be six, eight months, a year, more on." Caroline, 71 F, wife of person with MPM.

"Interviewer: *When you first heard about the trial, what were your thoughts?*

Kate: *Oh! Very hopeful because, it was hope… it was hope because we weren't so sad… sad isn't the right word. There was nothing, it's like an abyss isn't it?*

Interviewer: *And this was something?*

Kate: *It was. And if you see a trial, there is still that point where you can… there is an unknown. Oh my god, this could be a miracle! You don't know, do you! I was like, 'This is exciting', it's hopeful."*

Kate, 43 F, daughter-in-law of person with MPM.

2.4.2.5.3. Understanding the science

In line with earlier themes, people with MPM were well-informed about research. Several participants demonstrated an astute understanding of the biology of bacterial immunotherapy, and the ability to comprehend the scientific rationale behind the trial increased its appeal.

"I'm always interested in the most recent scientific data and if I think there's potential there, I would get involved." Frank, 81 M, person with MPM.

"As a layman I quite like the idea of taking something that is used to living inside you, some bacteria or other, and modifying it to make it a killer for what you want it to kill. That seems to me like a really good idea, if you can make it work, and that's the basis for which this thing was being sold, you could push this stuff down the catheter." Bob, 84 M, person with MPM.

"[You said] 'There's the TILT trial, there's the immunology that [is] being looked at.' And I said, 'Well, I didnt know anything about immunology', and I asked you to explain more about it, and I said, 'Oh! It's like small pox!'… And I said, 'I think I would like that to be part of the road that I would like to go down'. That seemed to make sense. I can get my head around smallpox. It, well it started of course with cow-pox. Immunising you against small-pox by giving you cow-pox. So I could understand that… It seemed to sort of relate, one to the other." Alan, 71 M, person with MPM.

Participants were also motivated to increase their own knowledge and understanding by participating in the trial, often reading up on the subject before deciding to take part.

"Well, I knew [husband] would follow it to the nth degree… He'll leave no stone unturned. He's looked at all the research papers and everything. He's done all the research and I'm happy just to sort of back him up. I'm interested, very interested, but he does all the research." Georgina, 79 F, wife of person with MPM.

2.4.2.5.4. Relatives' reluctance

Relatives were generally supportive of their family member's decision to participate in research.

> *"He's very up for going for things, and he wanted to help, and I supported him in that, as did our family." Caroline, 71 F, wife of person with MPM.*

> *"I'll back him up. Whatever he wants to do I'll back him up." Georgina, 79 F, wife of person with MPM.*

> *"Everything we do is a joint decision." Eleanor 81 F, wife of person with MPM.*

However, they also expressed a greater degree of reluctance regarding trial participation and were more likely to recognise the potential downsides of taking part.

> *"I wasn't keen for [husband] to be involved, to be honest... If he'd wanted, I would have gone along with it and supported him. It wouldn't have thrown me. I'm a very strong person and it wouldn't have thrown me at all, but I would rather he hadn't done it because I know he doesn't like being ill." Georgina, 79 F, wife of person with MPM.*

> *"I'm more reticent because I'm aware of what comes afterwards in so many of the options we've had." Caroline, 71 F, wife of person with MPM.*

The daughter of one participant explained how she had to consider the impact of the trial on her mother, as well as her father.

> *"But seeing him, well, I was worried that if he got, yeah, it's flu and whatever, but it was, also, I had to think about my mum, 'cause she's the one looking after him and it's taken its toll on her as well, so yeah. Obviously, I'd support whatever decision he made, but he did need to think of my mum as well. She's the one doing all the toing and froing" Janet 48 F, daughter of person with MPM.*

One relative expressed regret that her husband had participated in the trial:

> *"Interviewer: Do you wish [he] hadn't done it?*
>
> *Caroline: Sometimes, yes, sometimes."*
>
> *Caroline, 71 F, wife of person with MPM.*

The same person said that she would be reluctant for her husband to participate in research again unless there was a very clear benefit to him. For her, her husband's well-being took priority over any greater altruistic outcomes of research.

> *"I'd like to know what good it would do him really, at the end of the day…*
>
> *This sounds really selfish, but I don't want him to go through something that*

is going to shorten his life even more, if I'm honest." Caroline, 71 F, wife of person with MPM.

2.4.2.5.5. Synopsis

People with MPM were motivated to participate in research for multiple reasons, including altruism, a desire to further understanding of the disease and improve treatment options, and a wish to repay clinicians for their care. As with their clinical care, participants had a good understanding of the science behind the research and this increased their interest. Relatives, whilst supportive of their family members' decisions, tended to be more guarded about research, with a greater appreciation of the potential downsides.

2.4.2.6. Downsides of research participation

The first participant to receive the trial medication experienced an adverse reaction, during which time he reported feeling very isolated. In interview, he made several suggestions for improvement to the trial, the majority of which were implemented immediately via an amendment to the protocol (see Section 4.3.2.2.4.).

Other participants were generally positive about their experience of participating in the trial.

"I have no suggestions [for improvement], no, I think it was all good stuff" Bob, 84 M, person with MPM.

Participants' views differed regarding parts of the trial that they perceived as negative or in need of improvement. This was likely a reflection of the different personalities and priorities of the participants involved. There were no specific elements of the trial that were consistently reported negatively or were considered unacceptable by multiple people.

2.4.2.6.1. Timings

One participant felt that the time between consenting to receive the trial medication and it being administered was too short.

> *"My only concern was there was a very short time between having the IPC put in and actually doing the trial. The IPC went in [on a Wednesday and a week later] on the Thursday…you put the BCG in. I thought that was too quick… with hindsight." Alan, 71 M, person with MPM.*

However, his wife stated that she was comfortable with the amount of time they had been given to consider trial participation and with the scheduling of drug administration. She highlighted the urgency associated with administering treatment in MPM because of the short life expectancy.

> *"Bearing in mind what we knew about the MPM there wasn't really that window of opportunity to take a measured time over it. I think we both felt*

we'd had sufficient time to think about it." Caroline, 71 F, wife of person with MPM.

2.4.2.6.2. Organisation

The same person had concerns relating to organisational and logistical aspects of the trial. Her experience with her husband during routine medical appointments made her anxious that the trial would be poorly organised.

"I was worried about the chaotic way… when we come in for the meetings, when we come in for the consultations, invariably because so many people use that set of rooms, it's always chaotic as to getting the bloods, and this, and that, even something as simple as weighing somebody. It didn't instil me with confidence… I just thought if it's always as chaotic as this, how are they going to do the TILT treatment with [husband]?" Caroline, 71 F, wife of person with MPM.

Her concerns appeared well-founded as her husband was not satisfied with his experience of receiving the trial drug:

"Your procedure was very inadequate." Alan, 71 M, person with MPM.

Specifically, he felt the process was disorganised and poorly planned, which instilled doubts about the proficiency of the whole operation.

"You'd sort of get so far and then go, 'Oh! We haven't got a 3-way valve.' So someone would go off, probably [Nurse], and come back with a 3-way valve. And then you'd say, 'We're going to need some more saline, we haven't got enough' and then she'd go off and come back, and that didn't fill me with confidence." Alan, 71 M, person with MPM.

He suggested a run-through of the administration procedure would have improved the overall proficiency of the operation, something which was taken on board by the research team and will be implemented in future trials.

"I felt that you would have done better if you'd have a dry run. You didn't need me there. Get your team together, what are you going to do, make sure you've got all the equipment." Alan, 71 M, person with MPM.

It was possible that Alan's experience of receiving the trial drug was affected by the subsequent adverse reaction that he suffered. During her qualitative interview, his wife recognised the logistical difficulties inherent to any large organisations but emphasised that her priority was her husband. This highlighted, once again, the pattern of relatives adopting the role of protector on their husband's behalf.

"Yes, I'm less tolerant of what I perceive to be as inefficiency. Even though I appreciate with the NHS it's a very difficult thing to control, it's like a

monster machine that rolls along. I understand all the reasons, but I think when it's down to the individual you care about, that tolerance evaporates very quickly." Caroline, 71 F, wife of person with MPM.

2.4.2.6.3. Communication

Another concern raised by the same participant was that of communication. He stated that he would have liked more frequent contact with the research team.

"But we would have expected, well we did expect to have got a phone call from someone else. Even if it was a quick, "Oh hi, I'm phoning on behalf of [Doctor]. How are you?" Alan, 71 M, person with MPM.

However, others were satisfied with the amount of contact they had with researchers and with the amount of information they were provided.

"You know what I mean, [Doctor] was always quite informative but not to the extent of saying this will happen or that will happen, but was always, you know, kept me in the picture." Dave, 61 M, person with MPM.

Participants did not report any issue with additional visits to the hospital to complete trial assessments, even when asked directly.

"Interviewer: *You've had some visits for the TILT trial, you've been up to [hospital] a bit more often than you would have done if you hadn't been in the trial… How did you find that? Was that troublesome at all?*

Bob: *Not really, we are retired and it takes time, but as I've already said, we've found a way to do it easily by using Park and Ride."*

Bob, 84 M, person with MPM.

"Interviewer: *Coming to see us in the hospital, for some people that's quite a big deal and it's quite stressful. Would you say the same?*

Harry: *No, I wouldn't, no… It's the story of my life, in and out of hospital."*

Harry, 74 M, person with MPM.

2.4.2.6.4. Completing trial paperwork

Participants were asked about their experience of completing trial paperwork, including filling in the PROMs on a daily basis for three weeks. Most participants stated they did not find this task burdensome.

"Yeah, you know, those little tick sheets take half a minute, don't they? It is not like you are having to write a ten-page essay every day, no, it is nothing." Dave, 61 M, person with MPM.

One man did not particularly enjoy completing the PROMs as it drew attention to his lack of symptoms and made him feel like a charlatan. This echoed previous themes around the tendency of men with MPM to downplay their symptoms and look for the positives in their situation.

"Answering all the questions isn't one of my favourite occupations, because mainly the questions are asking me if I've got something wrong with this or this or this or this, and I haven't. I am a fraud!" Bob, 84 M, person with MPM.

2.4.2.6.5. Synopsis

In general, participants were positive about their experience of participating in the trial, with few mentioning any downsides or areas for improvement. One participant, who had a serious adverse reaction to the trial drug, described certain factors that worsened his experience, including a lack of communication with the trial team and a general sense of disorganisation. His wife felt similarly on many of these matters but had insight into the fact that her outlook had been influenced by her concern for her husband. Overall participating in the trial was acceptable to participants and relatives, although further focus was given to the acceptability of specific features of the TwiC design.

2.4.2.7. Specific TwiC features

The TwiC methodology was explained to participants during qualitative interviews and their thoughts elicited. Participants often commented spontaneously on the areas of the TwiC design that had been considered potentially beneficial for this population. In general, the rationale for choosing the TwiC design was validated by these comments.

2.4.2.7.1. Lack of placebo

Most participants were aware that clinical trials often included a placebo arm. Their views on the inclusion of a placebo in trials differed, with one person declaring that he would not wish to join a trial if there was a chance he would receive a placebo.

> *"I don't think I would have wanted to do a trial knowing that I would have been given a placebo." Dave, 61 M, person with MPM.*

Other people were more amenable to the idea, recognising the existence and potential benefits of the placebo effect.

> *"Years ago, I'd have said I'd like to know, and possibly I still would but I have seen the results of placebo as well, and that's put off the evil moment for a long time because the body did something, or the mind did something, and I think, it's something I don't understand, but it is very powerful in some cases. So if you say, yeah sometimes a placebo if you don't know it's a placebo, then I think you go with it because you think it's doing you good, and I think*

that control of your head doing it works." Caroline, 71 F, wife of person with MPM.

Most people were pleased that the intervention arm of the trial was open-label. Knowing that they had been selected to receive the trial drug reduced uncertainty and made the decision over whether to participate easier.

"What I did take from it from it… is that I was quite glad that, you know how trials are blinded, is that the right word? And therefore, you don't know if you are getting the placebo or not. I was quite glad to find out that actually you talked because I think that, I don't know, I think it would have made an impact. I think, again, that would have caused more conversations about if we should go for it or not. If he had come back and said, 'Oh yes, I can get on the trial but I don't know what I am having,' then I don't know if the outcome would have been the same." Kate, 43 F, daughter-in-law of person with MPM.

2.4.2.7.2. Blinding of controls

A key element of the TwiC design is blinding control participants to the existence of the trial. The justification for this is that it can reduce control patients' disappointment at not receiving the trial medication, particularly in conditions where treatment options are limited and people enrol in trials hoping to receive the intervention. This certainly

appeared to be the case in people with MPM as several participants admitted they had hoped to receive the trial drug.

"I signed up to the trial, or tried to sign up to the trial, for a number of reasons. The first was, looking at the data I had the impression that there could be an enhancement [in survival]." Frank, 81 M, person with MPM.

"Dave: I know you have to do a comparison, but I would not have been happy with a, well, just given a cup of tea…

Interviewer: So, you were in it to get the drug?

Dave: Yeah."

Dave, 61 M, person with MPM.

Unfortunately, it was not possible to maintain blinding of controls in TILT, and all participants were aware of the trial before randomisation. On finding out they had not been selected to receive the trial drug, unblinded control participants expressed disappointment, although this was handled with the usual stoicism and acceptance.

"He was so disappointed." Georgina, 79 F, wife of person with MPM.

"Yes, I was keen, but when the computer put me in the other side, even though I was keen I thought, 'Fate has put me in the other half', and that's it." Bob, 84 M, person with MPM.

Another potential benefit of TwiCs is reducing contamination if control participants, in their eagerness to receive the trial treatment, obtain it independently from the trial. Again, this appeared relevant to the MPM population, as one unblinded control participant explicitly asked whether he could receive the trial medication outside the trial.

> *"When [Doctor] looked at the computer and decided that I wasn't going to be on the trial, I said, 'Could I have the chemical added as a separate issue?'" Frank, 81 M, person with MPM.*

Another person believed he could request to be switched to the active trial arm if initially allocated to control.

> *"I put my name forward for [TILT] but I didn't get to be in the positive one, I was going to be a controlled one, although I'm sure they would have changed me." Bob, 84 M, person with MPM.*

If it had been successful, blinding of controls could have reduced the disappointment experienced by controls and the risk of contamination from participants seeking the trial treatment elsewhere. However, ethicists have discussed the potential harm associated with withholding information from control participants and the possibility of it damaging the clinician-patient relationship.(138, 144, 145) In this qualitative study, no-one

expressed concern about the possibility of being blinded as a control. Participants were happy to put their trust in doctors and be provided with information as determined by them. They did not feel that blinding would result in controls feeling deceived or misled.

> *"I think possibly, if you don't know about it, you're not losing out on anything." Caroline, 71 F, wife of person with MPM.*

> *"I put my faith in anybody. You know, I rely on absolutely everything [Doctor] said. If she tells me it is black, it is black." Dave, 61 M, person with MPM.*

2.4.2.7.3. Attrition

A potential problem with the TwiC design is participant attrition after randomisation. This is particularly pertinent to people allocated to the intervention arm who only hear about the intervention once randomisation has occurred. In TILT, one participant chose not to receive BCG after being allocated to receive it and another person declined to be followed up at the trial centre having been allocated to the control arm.

The participant who declined to receive BCG did so based on concern about side effects. Having had an IPC inserted, his breathing was the best it had been for some years and did not want to jeopardise this. His decision not to participate was not taken lightly, and he described feeling conflicted about it.

"Harry: When I got home,

Ida: Yeah, you did have second thoughts.

Harry: Yeah, I did… I told [Nurse] about the [trial] I backed out of… Well, I felt a bit guilty actually."

Harry, 74 M, person with MPM and Ida, 72 F, his wife.

The same gentleman was more than willing to continue participating in the observational cohort study and said he would be prepared to consider other trials of investigational medicinal products in the future, depending on how he was feeling at the time.

"If I can help in that way, then I will… I'd certainly try a new drug… Course I would, yeah, if I'm fit." Harry, 74 M, person with MPM.

However, it is important to note that despite Harry's wiliness to participate in future trials, a future TwiC would once again involve him being randomised before being told anything about the trial. Given his (very reasonable) wish to assess his physical condition at the time before deciding to join another trial, it's possible that he may choose not to participate again. For Harry, the decision to join a trial required contemporaneous assessment of his health and careful consideration of the risks and benefits of the trial intervention. In a standard RCT, this process would occur at the outset, but with the TwiC model it occur after randomisation has taken place. Harry was able to make an informed decision not to participate in TILT, but this happened once he

had already been selected to receive the intervention. This may have placed a greater emotional burden on him as he felt that he was actively "backing out" of a trial, rather than simply not signing up in the first place (as would be the case with a standard RCT).

The other participant who withdrew from TILT had been allocated to the control arm and was unblinded to this allocation. He was not interviewed as he was nearing the end of his life when he was invited to join the qualitative study. His daughter-in-law was interviewed and described his motivation for declining follow up at the trial centre.

> *"[Larry] had already said he can't see the point in this, because of going all the way down there and the impact on just going there… if it is not going to do anything." Kate, 43 F, daughter-in-law of person with MPM.*

She explained that because he knew he had been allocated to the control arm, he did not feel it was worth the effort to travel to a different hospital. She believed that he would have agreed to participate if he had been randomised to receive the trial drug.

> *"I do think if you had given the facts and he was getting the drug, he would have had it because he would have been very, 'I am going to try it and it's a trial,' so it's not like, erm, I think he would have tried it, I think he would have gone for it." Kate, 43 F, daughter-in-law of person with MPM.*

Although she was less certain, she also believed he would have agreed to participate had the trial been a blinded placebo-controlled RCT.

> *"If you do think you are offered something, are you going to miss out on it? Do you know what I mean? If you are offered [a trial] … even a placebo one, you are still offered that… and then you think, 'Well if I don't go for that, what am I going to get?'" Kate, 43 F, daughter-in-law of person with MPM.*

Kate was keen for her father-in-law to be considered for future trials, which was made possible with the TwiC methodology and Larry's ongoing participation in ASSESS-meso at his local hospital. She found this aspect of the TwiC design positive.

> *"I was worried about, then, if he wasn't on the list for TILT any more… would that mean that if any other trials came up he would fall through the net. And he went, 'Oh no no no, he has explained to me that actually you would stay on a register,' and I said, 'Well that's alright then.'" Kate, 43 F, daughter-in-law of person with MPM.*

However, if future trials were based at hospitals other than their local one, blinding would have to be breached in order to invite Larry up to the trial centre to undergo randomisation. It seemed probable that if he were allocated to the control arm again, he would make the same decision and decline to participate.

Certain elements of the TwiC methodology were implicated in both participants' decision not to participate in the trial. Although both people were keen to be considered for future trials – an opportunity that the TwiC design facilitated – if the same approach was used, the chances of further post-randomisation attrition seemed high. Clearly post-randomisation attrition is an important consideration with the TwiC design, particularly if it is to be used for trials with people with high symptom burdens, limited life expectancy, or using an interventions with a high risk of side effects.

2.4.2.7.4. Synopsis

Participants were pleased that the trial was unblinded, as this reduced uncertainty and helped with decision-making around participation. However, the failure to blind control participants led to some people feeling disappointed when they were not selected to receive the trial drug. This could have increased the likelihood of contamination between the trial arms, had the trial medication been available elsewhere. Other elements of the TwiC methodology may have contributed to the post-randomisation attrition of two participants. Overall, the TwiC design was considered acceptable by trial participants and their relatives.

2.5. Summary of findings

The qualitative study described peoples' experiences of having MPM and participating in the TILT trial, as well as that of their relatives. The identified themes related to both trial participants and relatives, although perspectives often differed between the two groups.

Some sub-themes have been described previously, including the stoicism of MPM patients, the importance placed on physical strength and the tendency of relatives to take on the role of advocates and fight of their loved one's behalf.(174) This study adds to the existing data by highlighting the importance placed on quality of life and the role this plays in decision-making. Another important finding was MPM patients' desire for certainty and difficulty accepting uncertainty. This had implications in the interpretation and understanding of risk, which in turn has important consequences for clinical and academic practice in MPM populations.

With one notable exception, experiences of trial participation were positive. The TwiC methodology was acceptable to everyone. People with MPM were found to be highly engaged and interested in research.

Chapter 6 – Discussion

6.1. Introduction

The final chapter of this thesis is in four parts. The key findings of the research are summarised with respect to the stated objectives of the thesis (section 6.2), before being interpreted in the context of the existing literature (section 6.3). The strengths and weaknesses of each work-stream are discussed (section 6.4) and finally, the implications for future research are considered (section 6.5).

6.2. Summary of key findings

The overall aim of this thesis was to explore the role of intra-pleural bacterial immunotherapy in MPM and to determine whether a full-scale trial of intra-pleural BCG or OK432 was warranted, feasible and acceptable. This was achieved via four specific objectives.

The first part of the research, and the first two objectives of the thesis, investigated whether bacteria in the pleural space were associated with longer survival in pleural malignancy. This question was addressed by reviewing the existing literature relating to intra-pleural bacterial products in MPE and by performing a population-level cohort analysis of survival in mesothelioma patients with spontaneous bacteria in the pleural space (pleural infection).

- *Key finding 1 – There was no strong evidence to support the hypothesis that intra-pleural bacterial agents are associated with longer survival in malignant pleural disease.*

- *Key finding 2 – Pleural infection was associated with higher short- and long-term mortality in people with mesothelioma.*

The second stage of the research and the final two objectives of the thesis focussed on the feasibility and acceptability of a randomised trial of intra-pleural bacterial immunotherapy in MPM, and of using the TwiC methodology to conduct a CTIMP in this population. Objective three addressed the feasibility element via a feasibility trial.

- *Key finding 3 – It was possible to design and execute a CTIMP using the TwiC methodology and to obtain the requisite approvals from the Research Ethics Committee, the HRA and the MHRA.*

- *Key finding 4 – The TwiC methodology was not suitable for trials in people with MPM, as blinding of control participants was rarely possible, recruitment was negatively impacted by attempts to maintain blinding and significant attrition occurred post-randomisation.*

- *Key finding 5 – Recruitment to the trial was challenging, due to fewer eligible patients with non-loculated effusions, expandable lung and functioning IPCs in situ than originally anticipated.*

- *Key finding 6 – Intra-pleural bacterial agents were associated with a significant local and systemic inflammatory response.*

The fourth and final objective of the thesis was to evaluate the acceptability of the TILT trial and the TwiC design to participants and their relatives. Qualitative interviews were performed to explore this, which yielded several other important findings about the experience of living with MPM.

- *Key finding 7 – People with MPM were highly motivated by quality of life rather than longevity and this influenced their decision-making with regard to systemic anti-cancer treatment and clinical trial participation.*

- *Key finding 8 – People with MPM valued certainty and were uncomfortable with uncertainty and unpredictability. This had important consequences around risk communication, in both clinical and research settings.*

- *Key finding 9 – Participants and their relatives were engaged and well-informed about MPM and about research. People chose to participate in TILT due to a combination of altruism, scientific interest and potential personal gain, and all participants found the TwiC methodology acceptable.*

- *Key finding 10 – For people with MPM and their relatives, thoughts of the future were associated with anxiety and grief for lost opportunities. Whilst people with MPM tended to be stoical, their relatives were less accepting and often took on the role of advocate for their family member. The specific needs of both groups should be catered for in the provision of routine clinical care.*

6.3. Interpretation of research findings

6.3.1. Intra-pleural bacterial agents and pleural malignancy: key finding 1

Key finding 1 – There was no strong evidence to support the hypothesis that intra-pleural bacterial agents are associated with longer survival in malignant pleural disease.

The systematic review found mixed evidence relating to intra-pleural bacterial products in pleural malignancy. Six studies reported a survival benefit associated with intra-pleural bacterial products, whilst eight found no difference. No specific bacterial product was more likely to be associated with a survival benefit and no particular underlying disease more likely to benefit.

There are several possible interpretations for the findings of this review. Firstly, the variety of products, doses and administration regimens used in the different studies may have obscured a genuine effect related to a single product or specific dose. Alternatively, there may be a consistent effect associated with all intra-pleural bacteria, but methodological issues with the studies meant they failed to demonstrate it. Finally, it is possible that intra-pleural bacterial agents have no association with survival in pleural malignancy.

With respect to the first point, it is accepted that different bacterial species and strains elicit differing degrees of immunological responses. For example, gram positive and gram negative bacteria induce different patterns of cytokine release with varying, and sometimes opposing, downstream cellular responses.(242, 243) Additionally, different

bacterial strains or preparations can have widely varying clinical effects, as has been demonstrated with different BCG preparations in bladder cancer.(244) It is plausible, therefore, that the lack of consistent effect noted for any single product could be a result of some studies, for example all of those with positive outcomes, using one strain whilst negative studies used an alternative, less immunogenic strain. Additionally, doses and administration regimens varied, with few bacterial products having an established optimal dosage. Apart from one RCT of OK432,(103) no formal dose-finding studies have been published for any of the bacterial products. This could have resulted in the use of sub-therapeutic doses with consequent apparent inefficacy or supra-therapeutic dosing with associated toxicity causing higher mortality.

An alternative explanation is that the studies failed to detect an effect that did exist. Small sample sizes and the fact that survival tended to be a secondary outcome measure meant that the majority of studies were under-powered to detect differences in mortality. In fact, several of studies were pilot projects with no formal sample size calculation undertaken. In the absence of meta-analysis, results from small individual studies should be interpreted with caution.

Finally, it may be the case that bacterial products have no effect on survival, despite good evidence that they are effective pleurodesis agents.(83) A similar effect was seen when chemotherapy drugs were administered intra-pleurally in malignant effusions – the drugs effectively caused pleurodesis but did not affect the underlying cancer or alter survival.(245-248) A theoretical explanation for this is that drugs administered into the

pleural cavity have limited absorption into the systemic circulation. This has been shown to be the case with intra-pleural fibrinolytics in empyema.(19, 249, 250) Since most MPE arise as a result of metastatic disease, with at least one tumour located anatomically distant from the pleura, a lack of systemic absorption following intra-pleural administration will limit exposure of distal tumours to the agent, limiting efficacy.

By this theory, intra-pleural drug administration would be an effective approach for localised pleural tumours i.e. MPM. Delivering the drug directly into the pleural space would result in high concentrations of the therapeutic agent in the precise area where its activity is required, whilst simultaneously reducing the risk of side effects from systemic absorption.(18, 246) The only study to investigate intra-pleural bacterial products in MPM was negative, although exclusion of 21 patients from the final analysis due to death, early progression of disease or loss to follow up put this study at critical risk of attrition bias.(182)

6.3.2. Pleural infection and survival with mesothelioma: key finding 2

Key finding 2 – Pleural infection was associated with higher short- and long-term mortality in people with mesothelioma.

The cohort study demonstrated that patients with mesothelioma were more likely to die after experiencing pleural infection, both in the immediate post-infection period and in

the longer term. This finding was in direct contrast to previous findings that survival was longer in patients with MPM and an IPC in situ who developed pleural infection.(186) However, the initial study was small and retrospective and may have been affected by recall bias. Alternatively, it may be that the presence of an IPC attenuated the risk associated with pleural infection by enabling regular pleural drainage and reduction in overall bacterial load, which was not the case for patients in the cohort study reported in this thesis.

The cohort study replicated findings from a similar population-level study undertaken in Canadian patients with lung cancer.(251) In that study, patients who underwent curative surgery and experienced an episode of post-operative pneumonia, empyema or mediastinitis had a higher mortality than those without post-operative infection (adjusted HR of 1.67, 95% CI 1.39–2.01). This finding may simply reflect worse outcomes in patients who experienced post-operative complications, but the similarity of the hazard ratio to that seen in the mesothelioma cohort supports the possibility of a genuine association between pleural infection and higher mortality.

Causality could not be determined from this observational study and for several variables the association with mortality may have represented a bi-directional or circular relationship. For example, although it is acknowledged that patients who underwent multiple pleural interventions were at higher risk of pleural infection, once infection occurred, they automatically required more interventions to manage it. As mentioned in Chapter 3, reverse causality may have applied to the primary outcome of the study,

i.e. it may be that dying patients were more likely to develop pleural infection, rather than infection being implicated in shortening their life.

In interpreting the results of the cohort study, it is important to recognise the distinction between statistical significance and clinical meaningfulness. The large sample size meant that a high level of statistical power was achieved, with p values below the 5% significance level for several analyses. However, p values provide no information on the size of an effect or its clinical relevance. For example, whilst the variable 'comorbidities' was associated with a statistically significant reduction in mortality ($p<0.001$), a HR of 0.99 is unlikely to represent a meaningful survival benefit. Additionally, the idea of a threshold p value of 0.05, below which results can be accepted as "true" is controversial. It is preferable to interpret p-values in absolute terms, as a measure of the strength of an association and the results of this study are best interpreted using this approach.(252) Importantly, the hazard associated with pleural infection in this study was both clinically meaningful and statistically strong.

Several of the findings from the cohort study were in accordance with previous observational work regarding prognostic factors in mesothelioma. Male gender and increasing age have been shown repeatedly to be associated with shorter survival,(1, 253) whilst being diagnosed during an acute or emergency presentation rather than in outpatient clinic is a poor prognostic indicator in several cancer types.(254) Meanwhile socio-economic position is a predictor of outcome in many medical conditions, both malignant and non-malignant.(255, 256)

It was anticipated that chemotherapy would be associated with enhanced survival, given its proven therapeutic role.(4, 5) That said, the overall survival benefit associated with chemotherapy was relatively small. This reflects the fact that for several years during the study period there was no standard of care chemotherapy for mesothelioma and ineffective agents were used, in the absence of any better options. Following the introduction of pemetrexed and cisplatin doublet regimen in 2008, survival outcomes improved. However, the mortality benefit seen in patients diagnosed after 2008 remained modest, due to the limited efficacy and low response rates associated with current chemotherapy regimens.(4, 47)

Regarding other treatment modalities, radiotherapy has no role in the radical treatment of mesothelioma, although it can be an effective measure for pain control.(1) The cohort data corroborated this. Surgery is rarely performed for MPM in the UK and RCT evidence has suggested it is associated with worse outcomes.(257, 258) The British Thoracic Society advocates against surgery apart from in the clinical trial setting; a recommendation that these data support.(1)

The longer survival associated with thoracoscopy and pleurodesis was likely to be the result of confounding. Thoracoscopy and pleurodesis are undertaken for diagnostic and symptom management purposes and do not have any disease modifying ability. The lower mortality associated with these interventions was likely to have resulted from 'confounding by indication', i.e. to be suitable to undergo thoracoscopy, patients must

be sufficiently fit, and this fitness determined their subsequent survival rather than the intervention. The corollary of this is that patients in whom thoracoscopy was contra-indicated (e.g. due to frailty) were more likely to be investigated via less-invasive pathways, i.e. percutaneous biopsies, and thus survival was worse in this group. Similarly, pleurodesis is generally undertaken in patients who are expected to live long enough for recurrent fluid to be a problem, whilst patients with shorter life expectancy are often treated with recurrent aspirations.

6.3.3. Applying the TwiC design to a CTIMP: key finding 3

Key finding 3 – It was possible to design and execute a CTIMP using the TwiC methodology, and to obtain the requisite approvals from the Research Ethics Committee, the HRA and the MHRA.

Prior to TILT, the TwiC methodology had been used to undertake trials relating to a range of research areas in multiple countries across Europe and North America.(197-199, 259) However, no CTIMP had ever been performed using the TwiC design. Given the increased regulatory requirements for CTIMPs, and specifically declaration 4.8.10(c) of ICH GCP that states all participants in a CTIMP must be informed about the IMP and the probability of being assigned to it, careful consideration was required when designing TILT to ensure the trial was fully compliant and legal.(202, 206) This was achieved by clearly separating patients into trial participants (people who had been randomly selected to the intervention arm and had consented to receive the IMP) and

control participants in the cohort (people who had been randomised to control and had not signed the TILT consent form).

The consequence of separating patients in this way was that all research activities needed to be clearly and precisely defined as either trial-related or cohort-related. By determining this at the outset, the protocols for ASSESS-meso and TILT were clear and explicit about what activities related to which part of the research. Additionally, the consent forms for each study contained specific points relating to the activities that would be performed as part of that study. For example the ASSESS-meso consent form asked participants to consent to undergo screening for future trials, to be randomly selected for trials and to allow their information to be used as comparison data for future trials, even if they had not been selected to participate. This created an unambiguous record of the activities each participant had agreed to undergo and a clear documentation of whether they were participating in the cohort study, the trial, or both. I believe this clarity facilitated the process of obtaining the necessary regulatory approvals, specifically from the MHRA.

Another approach that helped secure Research Ethics Committee approval was submitting the proposals for ASSESS-meso and TILT to the same committee and physically attending both meetings when the projects were discussed. The concept of TwiCs was discussed in depth at the initial meeting (when ASSESS-meso was under review) and the committee were able to resolve some minor concerns that they had about the design. Having an established understanding of TwiCs meant that when TILT

was reviewed by the same committee 2 months later, they were familiar with the idea and approved it with no further concerns.

I believe that TILT has set a precedent for future CTIMP TwiCs to follow. Since TILT began, I have been approached by several research teams around the UK who were designing and planning CTIMP TwiCs of their own. I have shared the TILT documents with these teams, and several of the trials are now up and running, having been granted the necessary approvals. Most recently, a large UK-wide COVID-19 cohort has been established as a resource for future TwiCs (COVIDENCE-UK - https://www.qmul.ac.uk/covidence/about-the-covidence-uk-study/). On the request of the PI of that study, I shared the TILT documents with the team and agreed for the exact same wording to be used in the COVIDENCE PIS and consent form.

6.3.4. Performing TwiCs in the mesothelioma setting: key finding 4

Key finding 4 – The TwiC methodology was not suitable for trials in people with MPM, as blinding of control participants was rarely possible, recruitment was negatively impacted by attempts to maintain blinding and significant attrition occurred post-randomisation.

One of the fundamental elements of the TwiC methodology relates to control participants not being informed about the existence of the trial. This mimics usual clinical care and aims to reduce the risk of disappointment if participants had been aware that they had not been selected to receive the intervention. Unfortunately, it

was not possible to blind control participants in TILT as all participants were aware of the trial prior to randomisation. Universally, this was a result of individuals' engagement with research processes and active enquiry about research opportunities.

Qualitative interviews with participants revealed that they were highly motivated with regard to their healthcare and well informed about current and potential future treatment options. Participants were actively supportive of research to advance mesothelioma care and would often seek out information about clinical trials in the hope of participating. Clinicians have reported similar experiences working with MPM patients on a day-to-day basis.(260) This created a quandary as, whilst high levels of patient activation are desirable, in TILT active patient engagement rendered blinding of controls impossible. Since no clinician or researcher would ever advocate for reduced patient activation, it seems that this element of the TwiC methodology is not achievable in MPM populations.

Additionally, attempts to maintain blinding of control participants (before researchers became aware that their efforts had failed) meant that the trial was not advertised on the clinical trial sections of websites such as Mesothelioma UK and Cancer Research UK. This limited recruitment from the wider MPM community. Similarly, whilst patients from other centres were screened for eligibility at the regional mesothelioma MDT, they could not be explicitly invited to attend the trial site to discuss the trial, as to do so would have unblinded them at the outset. This affected recruitment.

Although missing data was not a large problem in TILT, it appeared that data was more likely to be missing in control participants. In particular, no control participants returned the daily VAS booklet. Control participants were also more likely to have missed study follow-up visits. This could be a result of people being less motivated to attend study visits or complete the booklet because they did not realise they were providing data for the trial (or because they did and knew they were not in the intervention arm, so were disincentivised to complete trial data collection).

Alternatively, the fact that these people were officially only participating in the cohort study may have created confusion for research teams at recruiting sites. Although the protocol clearly stated that the follow up schedule for control patients must be altered to match the TILT regimen, it is feasible that research teams (and patients themselves) were established in the routine of ASSESS-meso follow up visits and failed to amend the research schedule accordingly. It is also possible that control patients were simply not recognised as providing comparison data for the trial. Either way, the lower data completeness rates was likely to be a result of controls not being officially labelled as trial participants. Since it was a necessary requirement in order to comply with clinical trials regulations that controls only participated in the cohort, the risk of lower quality data in the control arm must be acknowledged as a risk in CTIMP TwiCs.

Other elements of the TwiC methodology contributed to the lack of TILT feasibility. Because participants were randomised before being given any information about the trial intervention, one person randomised to IMP declined to receive it post-

randomisation. On qualitative interviewing, he revealed that he was concerned about the potential side effects outlined in the PIS, particularly because at the time of randomisation he felt better than he had for many years. Like many TILT participants and patients with MPM, he wished to prioritise quality of life over potential longevity.(48)

The magnitude and impact of post-randomisation attrition will vary depending on the nature of the trial intervention and the likelihood and severity of side effects. It is possible that a non-pharmacological intervention would be more acceptable to people with MPM, and a TwiC of such an intervention would be less vulnerable to post-randomisation attrition. However, given that all medications have some form of side effects, and anti-cancer agents are notoriously problematic in this regard, it seems that a CTIMP TwiC in MPM patients will inevitably suffer from some degree of post-randomisation attrition.

Post-randomisation attrition could have several undesirable consequences if it occurred in a full-scale trial. If many participants were to withdraw after randomisation, the study would be underpowered to detect the estimated effect based on the original sample size calculation. One way of addressing this would be to include in a larger "correction factor" in the sample size estimate to allow for potential attrition. Alternatively, recruitment could be continued until the target number of participants had received the intervention, rather than been randomised.

Post-randomisation attrition also introduces potential bias. Traditionally, RCTs are analysed on an intention to treat (ITT) basis, based on allocation at randomisation. However, with a TwiC, attrition is likely to affect the intervention arm disproportionately because people randomised to the control arm are not asked to provide further consent after randomisation and, therefore, have fewer opportunities to decline participation. The TwiC design enables outcome data to be collected on people who decline the intervention (assuming they agree to continue follow up in the cohort), so ITT analysis can be performed and can include the data of all participants randomised. However, differential attrition affecting the intervention arm could attenuate or negate a positive treatment effect, depending on how many people were included in the final analysis despite not receiving the trial agent.

An alternative is a per protocol (PP) analysis, where only the data of people who received the treatment to which they were allocated are used in the analysis. However, there are likely to be inherent differences between people who decline to participate in trials and those who agree, so excluding non-participators from the intervention arm but not the control arm (as they have not had the chance to decline participation) will again result in mismatched trial groups. Applying PP analysis to TwiC data is likely to result in an overestimate of the effect of the trial intervention, as “non-participators”, who are likely to have poorer outcomes generally, are still included in the control group but are excluded from the active arm.

Perhaps the most appropriate analysis plan to adjust for differential attrition in TwiCs is compliance-averaged causal effects (CACE) modelling, a form of instrumental variable analysis. Instrumental variable analysis allows estimation of the effect of an exposure on a chosen outcome, accounting for potential unmeasured confounding by the use of an unbiased instrument that independently predicts the exposure.(261) For example, in a clinical trial, allocation at randomisation (Z) is associated with exposure to the intervention (X) with no direct effect on outcome (Y) apart from via the exposure (Figure 6-1). The strength of the association between randomisation and intervention is influenced by the amount of attrition (A).

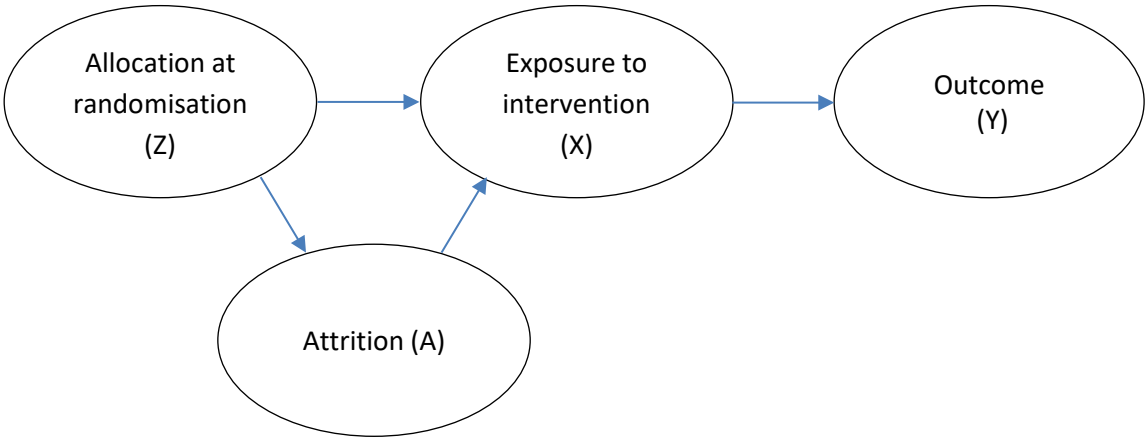


Figure 6.1 Instrumental variable analysis to estimate the effect of an intervention (X) on an outcome (Y), using allocation to randomisation (Z) as the instrumental variable. The relationship between allocation at randomisation and exposure to intervention is mediated by post-randomisation attrition (A).

To apply instrumental variable analysis to a TwiC, certain assumptions are required. Firstly, that a similar proportion of people in the control arm would have declined an intervention had they been offered one. Secondly, that theoretical non-compliers in the control arm would have similar characteristics to the known non-compliers in the intervention arm. Thirdly, that the act of being offered the intervention had no effect on

outcome. If these assumptions are valid, the proportion of people who would have declined participation in the control arm can be derived and their outcomes extrapolated from non-participators in the intervention arm. In this way, outcomes can be calculated for theoretically compliant controls and compared to outcomes of the known compliers in the intervention arm to generate an estimation of the direct effect of the intervention on the outcome (Table 6-1).(158)

a)	Intervention arm			Control arm		
	N	Events	Event rate	N	Events	Event rate
Compliers	900	90	0.1	?	?	?
Non-compliers	100	20	0.2	?	?	?
Total	1000	110	0.11	1000	150	0.15

b)	Intervention arm			Control arm		
	N	Events	Event rate	N	Events	Event rate
Compliers	900	90	0.1	?	?	?
Non-compliers	100	20	0.2	100	20	0.2
Total	1000	110	0.11	1000	150	0.15

c)	Intervention arm			Control arm		
	N	Events	Event rate	N	Events	Event rate
Compliers	900	90	0.1	900	130	0.14
Non-compliers	100	20	0.2	100	20	0.2
Total	1000	110	0.11	1000	150	0.15

Table 6-1 Worked example of CACE analysis a) Data collected during trial b) With extrapolated data for non-compliant controls in red and c) With derived data for compliant controls in red

Instrumental variable analysis of TwiC data was compared with ITT and PP approaches in a simulation study, using differing levels of non-participation.(156) The instrumental variable models were less biased than the other two methods at all levels of non-compliance. However, they suffered from lower power, as would be expected due to smaller participant numbers being used in the final analysis. PP and ITT both underestimated the effect size, whilst overestimates were noted with the instrumental variable approaches.

The different options for analysing TwiC data must be considered within the context of the overall research focus, specifically, whether a pragmatic or explanatory result is desired. As a pragmatic research method that aims to yield effectiveness data relating to real-world outcomes, it could be reasoned that ITT analysis is the correct approach for TwiCs. If a researcher wishes to know how many people would benefit from a certain treatment if it were widely prescribed in the general population, then an analysis that includes the outcomes of people who chose not to take the treatment, i.e. ITT, will provide that answer, with all the biases and confounding factors that would affect it in real life. A methodological purist might argue that applying the CACE analysis to TwiC data is an inappropriate attempt to extract efficacy outcomes from a pragmatic trial, rather than the effectiveness outcomes it is intended to supply.

In summary, certain elements of the TwiC design, such as blinding of controls and participants only being informed about the intervention after randomisation, were detrimental to participant recruitment and retention. Challenges in delivering these

aspects of the trial meant that TILT did not replicate the TwiC methodology in its truest form and, consequently, many of the expected benefits were lost. It is, therefore, not an ideal methodology to use for MPM trials.

However, rather than dismiss the TwiC methodology entirely in MPM, a modified TwiC approach may be workable in this population. Using an existing cohort to screen people for trial eligibility has obvious benefits in a rare disease that has patchy geographical distribution and patients who are willing to travel to be involved in research. There is scope to broaden the coverage of ASSESS-meso across the UK and to embed trial screening questions into the regular study visits. In this way, smaller, less research-active sites would screen patients at every visit and be alerted if someone were potentially eligible for a clinical trial elsewhere. They could then be offered the opportunity to travel to the trial centre to discuss the trial in greater detail. Since many RCTs of oncological treatments in MPM have similar eligibility criteria, the screening questionnaire would not be particularly onerous or time-consuming.

Equally, there is no reason not to embed a standard double-blind RCT design within an existing cohort. This would remove several of the TwiC feasibility issues identified during TILT, as well as removing the methodological gymnastics required to ensure the TwiC complies with CTIMP regulatory requirements. By embedding an RCT within a cohort, certain TwiC benefits could be maintained, for example data collection on people who withdraw from the trial and collection of long-term outcome measures, e.g. survival, without the need for long (and expensive) trial follow-up.

6.3.5. Recruitment and eligibility: key finding 5

Key finding 5 – Recruitment to the trial was challenging, due to fewer eligible patients with non-loculated effusions, expandable lung and functioning IPCs in situ than initially anticipated.

When TILT was initially designed, there were no data available to inform estimates of eligibility within the MPM population. Specifically, nothing had been published relating to the proportion of people with MPM who were not actively receiving chemotherapy, nor on the number of MPM patients who had an IPC in situ in the absence of non-expandable lung (NEL). Hence, it was difficult to estimate the proportion of patients with MPM that would meet the eligibility criteria for TILT and recruitment rates were hard to predict at trial initiation.

After the study opened to recruitment, two papers were published reporting relevant data. The first described the number of MPM patients who were eligible for chemotherapy but chose not to receive it. Of 139 patients offered first-line chemotherapy, 46 (33.1%) declined to receive it, opting for conservative care instead.(48) These people would have been eligible for TILT upon making that decision, relatively early in their disease course, but the remaining 66.9% would not.

The second study, published after TILT opened to recruitment, reported the presence of pleural effusions, with and without NEL in a clinical cohort of patients with MPM. As expected, pleural effusions were commonplace, occurring in 83% of people at diagnosis, but the prevalence of NEL was considerably higher than previously expected, occurring in 33% of people with effusions.(39) Just 55% of people with newly-diagnosed MPM had a pleural effusion with expandable lung.

A rough calculation based on these two papers revealed that just 18% of people with MPM were eligible for TILT at the point of diagnosis, based on the chemotherapy and NEL criteria alone. This pool of potential participants would be reduced further following application of the remaining eligibility criteria, although to what extent cannot be predicted. Whilst the pool of potentially eligible people may have been boosted by patients later in their disease course who had completed frontline chemotherapy, this relies on their performance status and predicted survival still meeting the necessary inclusion criteria. In reality, this cohort is unlikely to be particularly sizeable.

If a full-scale trial of intra-pleural immunotherapy were planned, these influential eligibility criteria would have to be given due consideration. A compelling safety argument can be made for avoiding chemotherapy whilst administering live bacteria to patients. All chemotherapy agents are potent immunosuppressors and carry a high risk of neutropaenia and associated sepsis.(262) Combining this with administration of live bacteria could expose patients to significant harm. Hence, ongoing or recent receipt of chemotherapy would have to remain an exclusion criterion in a full-scale trial.

Although agents can be delivered into the pleural space in the absence of an IPC, e.g. using pleural aspiration equipment, the inevitable inflammatory response caused by intra-pleural bacterial agents and the resultant increase in pleural fluid production means that some form of drainage is necessary in the days following administration. The options for managing this include inpatient admission for a temporary chest drain or outpatient management with an IPC. The latter seems favourable in the palliative population and given the risks associated with inpatient hospital stays. Therefore, an IPC is a pre-requisite for intra-pleural bacterial immunotherapy. However, this does not necessarily mean that the patient must have a pleural effusion at enrolment. Previous studies have inserted IPCs into patients with minimal or no effusion in order to deliver intra-pleural agents.(263-265) However, this requires thoracic surgery, which not all patients will be suitable for. For example, at least two TILT participants were not medically fit enough to undergo a general anaesthetic. Therefore, widening the inclusion criteria to people without an effusion who could undergo surgical placement of an IPC is, again, unlikely to dramatically increase the number of eligible patients.

The emergence of IPC management methods that prioritise pleurodesis, e.g. daily drainage regimens and talc slurry delivery via IPCs, is likely to result in a further reduction in the number of people who have a functioning IPC in place for a sustained period of time.(41, 266) This will place additional limitations on recruitment to a full-scale intra-pleural bacterial immunotherapy trial.

Finally, developments in the field of MPM treatment since TILT was initiated are likely to impact on recruitment to a future full-scale trial. In April 2020, there was a pivotal breakthrough relating to first-line therapy for MPM, in the form of the CheckMate-743 trial.(267) This phase III RCT compared standard chemotherapy (pemetrexed and cis/carboplatin) with a combination of two immune checkpoint inhibitors (ipilimumab and nivolumab) and showed a clinically meaningful extension in overall survival in the immunotherapy arm. The full paper is awaited and, once published, a thorough evaluation will be necessary to determine whether the survival benefit outweighs the potential toxicity associated with combination ICI. However, this trial is likely to lead to a change in the standard of care for frontline treatment of MPM. This could negatively impact on the number of patients eligible for a full-scale trial as more people are likely to accept frontline immunotherapy than chemotherapy. Additionally, the safety of treating people who have received prior immunotherapy with further immunotherapy at a later date is unknown. Most immunotherapy trials excluded people who had received prior immune-based treatments and therefore offering intra-pleural bacterial agents to people after frontline immunotherapy is not advisable.(17, 49-51, 82)

6.3.6. Clinical responses to intra-pleural bacterial agents: key finding 6

Key Finding 6 – Intra-pleural bacterial agents were associated with significant local and systemic inflammatory responses.

All three participants who received an intra-pleural bacterial agent experienced remarkably similar systemic inflammatory responses. The response began within 1 day of IMP administration and consisted of an increase in chest pain and breathlessness, with fevers and sweats occurring some days later. The reaction was accompanied by a rise in serum inflammatory markers. Usually the reaction resolved within a fortnight with simple analgesia and anti-inflammatory medication, however for one participant, symptoms persisted for the remaining 12 weeks of the study and a prolonged course of oral steroids. Two participants experienced reactions of such severity that hospital admission was necessary.

This type of reaction is consistent with a cytokine release syndrome (CRS). The syndrome describes a constellation of symptoms that result from the rapid release of inflammatory cytokines into the bloodstream following activation of immune cells, specifically T cells. It is increasingly recognised as a potential complication of immunotherapy. Classical symptoms and signs include fevers, breathlessness, nausea, fatigue and malaise, tachycardia and deranged liver function, all of which can range from mild to life threatening in severity.(268) Unfortunately, and somewhat counter-intuitively, neither the presence of CRS nor the severity of the reaction appear to correlate with clinical response to immunotherapy. Data from the field of haematological malignancies (where immunotherapy has revolutionised the treatment landscape) have described many patients who experienced complete remission with no overt symptoms of CRS, and just as many who developed severe CRS in the absence of any appreciable tumour regression.(269)

The reaction observed in TILT participants who received intra-pleural bacterial agents was also reminiscent of the pleural inflammatory effects seen with several pleurodesis agents.(270) A network meta-analysis of interventions for MPE reported that all agents induced some degree of fever, chest pain and breathlessness following instillation into the pleural cavity.(271) Essentially, anything that causes irritation of the pleural mesothelium leads to the release of chemokines such as interleukin-8 (IL-8) that attract neutrophils to the pleural space. The presence of activated neutrophils induces the mesothelium to secrete further pro-inflammatory cytokines, such as TGF-β and basic fibroblast growth factor, which perpetuate the inflammatory pathway.(272)

It was, therefore, unsurprising that combining a non-selective immunotherapeutic agent with intra-pleural administration led to profound local and systemic CRS and inflammatory responses. Similar reactions have been described following intra-pleural administration of oncolytic viruses and viral vectors for gene therapy in people with MPM. A phase I trial of intra-pleural adenovirus vector encoding human IFN-α (Ad.IFN-α2b) required dose-reduction after the first 3 patients treated all experienced severe flu-like symptoms with high systemic and pleural interferon-α (IFN-α) levels.(273) Symptoms began within 8 hours of administration and, in some patients, lasted for 7-10 days. The subsequent 6 participants, treated with a lower dose, similarly experienced fevers and tachycardia but to a more tolerable degree.

The subsequent trial of Ad.IFN-α2b added an anti-inflammatory medication in the form of 14 days of celecoxib (a COX II antagonist) to be given alongside the viral vector.(263) Despite this, there were 39 episodes of CRS recorded in 40 participants who received the Ad.IFN-α2b, although all were mild, with no events more serious than Grade 2. Most CRS symptoms resolved within 48 hours. However, 8 participants declined to receive a second dose of Ad.IFN-α2b due to the side effects of the initial administration. The researchers identified a sub-group of participants who experienced mild but persistent symptoms of malaise, anorexia and low-grade fevers that endured for several days. This was assumed to be secondary to systemic effects of IFN, based on the similarity with side effects seen when intravenous IFN was used in other conditions.

Another study used an oncolytic mutant of herpes simplex virus administered intra-pleurally.(274) Analysis of pleural fluid samples from the first 9 patients revealed increased levels of interferon γ (IFN-γ), TNFα and interleukin 6 (IL-6) in most people, as well as the IFN-γ associated cytokines IFN-γ-induced protein 10 (IP-10) and monokine induced by IFN-γ (MIG). Some participants also demonstrated rises in pleural fluid concentration of VEGF, interleukin 2 (IL-2), interleukin 10 (IL-10) and interleukin (IL-12) after virus administration, but these responses were less consistent.

Future trials of intra-pleural immunotherapies should be aware of the likely systemic inflammatory response/CRS associated with their use. Participants should be counselled about the risk of this side effect, particularly participants with MPM in light of their preference to prioritise quality of life (see key finding 7). Researchers planning such

trials should consider the addition of a regular anti-pyretic, with or without a concurrent anti-inflammatory to mitigate the risk and severity of possible inflammatory reactions.

6.3.7. Patients' priorities with mesothelioma: key finding 7

Key finding 7 – People with MPM were highly motivated by quality of life rather than longevity, and this influenced their decision-making with regard to systemic anti-cancer treatment and clinical trial participation.

Several participants in TILT had chosen not to receive chemotherapy, despite being medically suitable to receive it. Universally, this decision was based on a desire to maintain quality of life and concern that chemotherapy side effects would impact negatively on this. This was combined with an appreciation that chemotherapy was associated with relatively limited survival benefit in MPM, and therefore the risk-benefit balance was not in its favour.

This finding replicated an earlier observational study from our centre describing the characteristics and motivations of people with MPM who declined chemotherapy. Of 139 patients offered chemotherapy, 46 (33.1%) chose not to receive it.(48) Reasons included concern that the benefits of chemotherapy did not outweigh the risks of treatment, and patients who were asymptomatic wishing to maintain their quality of life rather than jeopardise it with chemotherapy side effects.

Initially, this decision seems justified, as chemotherapy has been shown to impact negatively on certain symptom-specific aspects of quality of life. In another observational study from our group in Bristol, people with MPM who were receiving chemotherapy reported higher scores for nausea, vomiting, alopecia and sore mouths, as well as lower global health and social function scores during treatment, compared with patients who had elected not to receive treatment.(275) In contrast to the beliefs of participants in TILT, however, symptoms did not affect quality of life, which remained stable over the 16 week study period. Furthermore, quality of life improved in people who responded to chemotherapy, presumably due to a combination of improvement in tumour-related symptoms and the heartening knowledge that they were responding to treatment. However, it is worth noting that patients were relatively symptomatic at baseline, so it is not known whether the same improvements would be seen in asymptomatic people with MPM who received chemotherapy. Equally, the longer-term impact of chemotherapy on quality of life is not known.

Recent oncological trials in MPM have also included quality of life outcomes. In the phase III randomised MAPS trial, 36% of 225 patients who received standard pemetrexed and cisplatin chemotherapy reported a deterioration in their global quality of life after 9 weeks of treatment, as did 30% of the 223 patients who received chemotherapy plus bevacizumab.(6) Whilst similar numbers of people experienced improvements in their quality of life, (27% and 29% for chemotherapy and bevacizumab/ chemotherapy respectively), these data demonstrate the element of

speculation inherent to the decision to embark on systemic anticancer therapy. As this thesis shows, some people with MPM are unwilling to take this gamble.

The survival benefit of two to three months offered by chemotherapy in MPM was not deemed worth the risk of side effects by TILT participants. In the literature, there is significant variation in the overall benefit that is perceived sufficient to make chemotherapy worthwhile.(276-279) In interviews with 83 women with early breast cancer, in which women were presented with four validated, hypothetical, trade-off situations, Duric and colleagues discovered that over 50% would be willing to receive adjuvant chemotherapy in exchange for a survival benefit of just 1 day.(280) Tellingly, 51 of these women had a dependent child or children, and this factor was strongly associated with the likelihood of accepting smaller survival benefits. Several women stated that "*every day matters, especially because of my children*".

Age differences and stage-of-life differences between people with MPM and women with breast cancer may explain their contrasting opinions on the benefits required to make chemotherapy worthwhile. However, a systematic review by Jansen et al examining the determinants of uptake of adjuvant chemotherapy (i.e. chemotherapy given after curative tumour resection) did not find age or type of cancer to be related to decision-making.(278) However, as a cancer with no surgical or adjuvant chemotherapy options, no people with mesothelioma were included in the review and the findings may not be completely comparable with chemotherapy given in the first-line setting and with palliative intent, as with MPM.

Toxicity and the risk of side effects have been shown to play a large role in patients' decisions around chemotherapy with other cancer types. In their systematic review, Jansen et al demonstrated that people were more willing to accept chemotherapy with fewer side effects, and would generally do so for a lower chance of a cure.(278) When Irwin and colleagues presented 46 women with breast cancer with a choice between chemotherapy regimens, impact on quality of life and side effect profile were two of the most important factors affecting their decision-making.(281) Overall, therefore, people with MPM appeared to have similar priorities to other people with other cancers and were influenced by the same factors when making decisions about whether to receive chemotherapy.

The decision to participate (or not) in TILT was also influenced by the desire to maintain quality of life and minimise the risk of side effects. This also corresponded with clinical trial decision-making in patients with other cancer types. A systematic review of 51 studies evaluating the factors affecting research participation in people with cancer found that 19% reported "concern about side effects" as a key factor in patients' decisions not to participate in a trial.(282) Anxiety about the trial intervention (which presumably involved a degree of overlap with concern about side effects) was noted as a factor in the decision in 25% of studies. In one study that was included in the systematic review, people with different cancer types were asked to complete a questionnaire in which they scored how strongly they agreed or disagreed with certain statements.(283) Of the 51 people who had declined to participate in a trial, 88.2% stated that the side effects of the trial treatment outweighed the benefits.

Interestingly, oncologists were less concerned about side effects, and appeared to underestimate their importance to patients as a deciding factor in clinical trial participation. In a survey of 137 oncologists and 170 patients, patients ranked the fear of side effects as the most influential factor in their decision whether to join a trial, whilst oncologists ranked it fifth (out of seven possible options).(284) Oncologists were not interviewed as part of TILT, although this would be an interesting avenue for future research, particularly given the toxicity profile of many of the new combination immunotherapy regimens being investigated in MPM.(15, 17)

The findings of this thesis suggested that, in keeping with studies of people with other cancer types, people with MPM placed great emphasis on the risk of side effects when deciding whether to participate in clinical trials. The importance of quality of life to people with MPM, and their resultant disinclination to risk side effects should be noted by clinicians and triallists, and taken into consideration when planning future clinical trials and in communicating with patients, both about trials and about planned treatments.

6.3.8. Communicating uncertainty and risk: key finding 8

Key finding 8 – People with MPM valued certainty and were uncomfortable with uncertainty and unpredictability. This has important consequences around risk communication, in both clinical and research settings.

The qualitative study highlighted that people with MPM sought certainty and were frustrated by perceived ambiguity. In part, this reflected their high levels of engagement and pursuit of knowledge about all elements of their condition. Equally, the fondness for numerical values and statistical expressions of probability was potentially grounded in their occupational backgrounds. As a whole, men with MPM had worked in professions dictated by numbers and precision, e.g. engineering, plumbing, construction. It was predictable, therefore, that they should feel comfortable in the realm of figures and would seek recourse to that domain wherever possible. (Clearly this is association rather than causation; it is equally possible that job choice was influenced by a pre-existing enjoyment of numbers rather than numerical familiarity being a result of vocational experience. However, the end result remains the same, these were men with a preference for and familiarity with numerical information).

A wish for certainty and discomfort with uncertainty is not specific to men with MPM, though. As Keren and Gerritson described in their experiments, aversion to ambiguous information is a universal human trait and one of the most consistent determinants of decision-making behaviour.(285, 286) However, people with MPM were subject to several other factors that could have increased their wish for certainty, specifically the incurable nature of their disease.(287)

Receiving a diagnosis of a chronic or terminal condition has been described by Michael Bury as a 'biographical disruption', in which the structures and routines of everyday life

are thrown into disarray.(287) The future story of that person's life is abruptly changed, requiring complete re-evaluation. In their seminal book about awareness and dying, Glaser and Strauss discuss the various types of 'work' that need to be done to achieve acceptance of death.(288) This includes 'biographical work', in which a person's life story is reconstructed to account for and encompass the new future. When a person's plans for the future, which have strengthened in certainty over years of their life, are suddenly removed, the desire to replace them with something equally concrete is understandable. Unfortunately, a fundamental part of biographical disruption is the unavoidable uncertainty that comes with it.

Uncertainty comes in many forms, and the word itself can refer to an internal emotion or an external state of affairs. Internal or psychological uncertainty is the feeling a person experiences if they lack information or have an unresolved decision. Psychological uncertainty is the personal experience of not knowing and the emotion associated with that experience. Most human beings are inherently averse to the sensation of psychological uncertainty.(286)

Psychological uncertainty can be created by external uncertainty, i.e. it may be an awareness that objective information or knowledge is lacking. Fox and Ülkümen described two types of external uncertainty – epistemic and aleatory.(289) Epistemic uncertainty is uncertainty relating to numbers, facts and science due to limited knowledge, and is the main uncertainty that men in this study were trying to overcome. Epistemic uncertainty is a dynamic state, as there is a possibility that the knowledge gap

could be filled in some way or at some point in the future. This is in contrast to aleatory uncertainty, where unknowns are a result of randomness or chance and can never be predicted or converted to certainty, for example the uncertainty of where a roulette ball will land on its wheel.

People in our study were exposed to both types of uncertainty: aleatory uncertainty relating to the date of their death and their individual trajectory over future months, and epistemic uncertainty about whether BCG was an effective treatment option for MPM. These uncertainties overlapped in that they both related to survival and, sadly, neither uncertainty would be addressed for these participants during their lifetime. However, it is possible that the uncertainty about BCG efficacy could be resolved at some point in the future following further research, hence it represented a form of epistemic uncertainty. In contrast, the ability to predict the exact date of someone's death is unlikely to ever be possible, hence that uncertainty is aleatory.

Participants were also exposed to a combination of aleatory and epistemic uncertainty in regard to the adverse reactions experienced during the trial. Whilst information was available about the likelihood of an adverse reaction and what form that reaction could take, the absolute (epistemic) figures were not known. Added to that was the aleatory uncertainty of how severe the reaction might be for a specific individual and whether it would ultimately shorten or lengthen their life. Although men in the trial were provided with written and verbal information to try and reduce the epistemic uncertainty as

much as possible, this was perceived as insufficient, probably because the aleatory uncertainty remained unaddressed.

In clinical research, particularly where investigational medicinal products are involved, uncertainty is inextricably linked with risk. According to Steven Sloman's Dual Process Theory, risk and the response to it can be processed in two ways; analytically or emotionally.(290) Emotional processes are usually dominant, as an evolutionary remnant from when risk decisions were required quickly and in high stakes situations. These instinctive reactions remain at the forefront of our risk assessment processes, and continue to play the biggest role in decision-making.(291) It was interesting to note, therefore, that men with MPM tended to be less emotional, demonstrating a highly pragmatic and analytical approach to their disease and decision-making. Had they suppressed their emotional risk response in favour of the analytic pathway, and this was why they were disappointed when they subsequently experienced harm?

The qualitative findings raised important questions about communication of risk, which had implications for both clinical and academic work. Men in this study described experiencing "unexpected" adverse reactions, despite having been provided with information beforehand that detailed the possibility of a reaction. In clinical practice, we routinely provide people with information about procedures and treatments that have potential side effects or risk of complications. Is that information sufficient and do patients feel adequately forewarned if they subsequently experience a complication? The findings of this thesis would suggest not.

How can this communication gap be addressed? It is our duty as doctors and researchers to ensure that patients and participants are fully informed before we subject them to any clinical procedure or academic process. However, communicating uncertainty is complex and is made up of multiple elements that contribute to the eventual outcome. Van der Bles and colleagues summarised the complexity of the process when they noted that the seemingly straightforward task of imparting information from one person to another actually involved multiple factors, namely *who* is communicating *what*, to *whom*, in *what form* and to *what effect?*(285) These factors will be considered in turn over the remainder of this section.

In a clinical trial or medical procedure, the '*who'* is usually pre-determined and unchangeable. The responsible clinician or researcher should ensure they appreciate the complexities of risk communication specific to the relevant population and take every possible measure to ensure the communication is successful.

The '*what'* of risk communication should also be clear in terms of the object to which the uncertainty relates (in this study intra-pleural BCG, in other studies the trial intervention). However, to fully understand the '*what'*, further interrogation is required. What is the source of the uncertainty and to what level does it relate? For BCG, the uncertainty arose from an absence of established knowledge about its effects when used intra-pleurally. But this wasn't due to an absolute lack of information; published reports have described the use of intra-pleural BCG since the 1970s. These

papers reduced the level of uncertainty a little, by providing some information about the effects of BCG. However, the studies were poorly reported and did not provide robust data that could be applied to the current trial, hence a moderate level of uncertainty remained.

When designing a clinical trial, the degree of uncertainty relating to the intervention is established during the early research phases when the existing scientific literature is reviewed and evaluated. In clinical research, this uncertainty informs equipoise and is usually the primary motivation for performing a trial. In contrast, for clinical procedures and established treatments, the evidence base is generally stronger and the level of uncertainty about the intervention lower. However, clinicians are still required to familiarise themselves with the literature and evaluate its strengths and weaknesses in order to communicate an accurate level of risk to their patients.

The next consideration relates to *how* uncertainty is communicated. The manner in which the communication takes place should span media, i.e. paper-based, verbal, web-based, etc. to ensure maximum appeal and accessibility, whilst the content will depend on the information available. Numerical data are often helpful and pictorial representations alongside numbers can enhance understanding.(292) However, interpretation of numerical risk can depend on how it is presented, as demonstrated in one study by Slovic and colleagues. They presented experienced forensic psychologists with a theoretical case of a patient with a psychiatric diagnosis whose risk of performing a violent act was estimated to be 10%.(293) More psychologists were willing to

discharge the patient into the community when the risk was described as a probability (i.e. “Patients similar to Mr. Jones are estimated to have a 10% chance of committing an act of violence”) than when it was described in terms of the actual frequency of the event happening (i.e. “of every 100 patients similar to Mr. Jones, 10 are estimated to commit an act of violence”). They hypothesised that risk presented as a probability created a benign image of an individual who was unlikely to harm anyone, whilst reporting frequencies of actual events caused people to imagine the events and these “affect-laden images” created a higher perception of risk. For people with MPM, the latter approach may be preferable as it could encourage people to imagine the reality of experiencing an adverse reaction and its potential impact on them as an individual.

Risk communication becomes harder where numerical data is not available. In these situations, verbal descriptors such as “rarely” and “likely” are required. However, whilst these labels feel more natural to use in conversation and may be easier for people to understand, their interpretation is highly subjective. Interpretation of verbal descriptors of risk can vary both between people, depending on their particular frame of reference, and within individuals depending on the circumstances and context.(294, 295)

The people *to whom* uncertainty is being communicated cannot be changed in a trial or clinical setting. It is important, therefore, to understand the characteristics of the population involved and appreciate how those characteristics may influence how the communication is received. Perception and understanding of uncertainty varies depending on an individual’s experience, expertise, numeracy skills, educational level

and general degree of optimism.(285) Prior or existing attitudes and beliefs are also important as people are more likely to assimilate uncertainty that concords with their own beliefs.(291) The findings of the qualitative study provided important insight into how people with MPM process information, and made a strong case for presenting uncertainty and risk clearly and in numerical form wherever possible. In a clinical trial, this approach could be used to address factual (epistemic) uncertainties, but since the ultimate aleatory uncertainty about survival persists, perhaps this too should be tackled explicitly, for example with the following statement:

> *"We do not know what effect this drug will have on you personally or on your underlying disease. This leaflet contains the current knowledge that exists about this drug, but there is still an inherent uncertainty involved with participating in this (or any) trial."*

Being overt and upfront about uncertainty may appeal to people with MPM who preferred their doctors to be direct, clear and upfront when delivering information.

The final consideration in communicating risk is the *effect* of the communication. For potential trial participants to be fully informed, knowledge of the potential risks must be accompanied by an appreciation of how those risks apply to them. Assimilating information about risk is an individual process that varies depending on people's backgrounds, experiences and belief systems.(291) This highly personalised process can be particularly challenging in a clinical trial where the trial requirements may prioritise academic rigour over individual clinical need, for example the use of a placebo or

blinding of clinicians to the treatment their patients are receiving. Many people, including several TILT participants, struggled to appreciate that trial participation may limit the degree of personalised care they receive, a phenomenon that Appelbaum and colleagues labelled the "therapeutic misconception".(296, 297) As a result of this phenomenon, people consistently underestimated the risks associated with participating in research, whilst overestimating the potential benefits.(298-300) A specific and frequent manifestation of the therapeutic misconception was the belief that a trial intervention would only be offered if it carried some potential benefit and would not be offered if it was associated with significant risk.(300) This belief was expressed by several participants in TILT and their relatives.

In this study, the surprise and distress described by participants who experienced a reaction made it clear that risk communication had been unsuccessful. If the above considerations and interventions are implemented, future trials may avoid this pitfall.

6.3.9. Research participation and the TwiC methodology: key finding 9

Key finding 9 – Participants and their relatives were engaged and well-informed about MPM and about research. People chose to participate in TILT due to a combination of altruism, scientific interest and potential personal gain and all participants found the TwiC methodology acceptable.

Surveys undertaken by the charities Mesothelioma UK and the British lung Foundation (BLF) in 2012 and 2013 demonstrated that people with mesothelioma were keen to know about research and to participate wherever possible.(301, 302) This, alongside the enthusiasm to participate in patient support groups and PPI events,(260, 303) illustrates an engaged and motivated patient group.

An active approach to information gathering can be a useful coping strategy and has been shown to reduce anxiety levels and increase feelings of control in people recently diagnosed with cancer.(304, 305) Cassileth et al asked 256 people with a diagnosis of terminal cancer to complete an assessment about their information level, followed by a survey about hopelessness.(306) They found that people who were well-informed about their condition were more likely to be hopeful about the future, regardless of their expected prognosis. Most people expressed a wish to be provided with as much information as was available, and for communication to be open and honest.(306) Similar feelings were expressed by 56 patients receiving palliative care for a terminal diagnosis who completed a Likert scale questionnaire about their information needs.(307) 100% of patients wanted their doctors to be honest, 98.2% wanted to be informed about changes in their disease status, 89.3% wanted to know about new treatment options and 80.4% wanted to be told the expected course of their disease.(307) This corresponds with the conclusion of this thesis regarding the information requirements of people with MPM.

It must be noted, however, that not everyone is as eager for information as the people described in the above study. Some people may find it upsetting to be reminded of the short life-expectancy associated with MPM,(260, 308) and indeed one of the participants in TILT (who unfortunately died before she could participate in a qualitative interview) was adamant throughout her diagnostic and treatment journey that she did not wish to know her prognosis. Previous qualitive work with people with mesothelioma has highlighted the varying amounts of information that different patients desire and are able to process.(232, 308) In line with the findings of this thesis, however, most people expressed a wish for honest and direct communication.(232)

There is a clear tension here, in how to balance honesty and appropriate information transfer with the preservation of hope and optimism. The same issue was raised in the questionnaire study mentioned above, where despite 100% of patients stating that they wanted honesty from their doctors, 91% also wished their doctors to be optimistic.(307) Is it possible to be optimistic when communicating about a terminal disease with limited treatment options, like MPM? Probably, as long as information is provided in a caring manner, rather than abruptly and with a sense of the physician "washing their hands" of the patient.(304) The RADIO-meso study confirmed this. Patients with MPM were interviewed about the experience of receiving the diagnosis and many commented that the shock of the news was mitigated if it was communicated in a warm and sensitive fashion.(232) Respondents to the Mesothelioma UK patient survey described similar experiences, whereby the sensitivity of the staff helped relieve some of the trauma of receiving the diagnosis.(301) Maintaining the patient at the centre of communication,

being led by their information requirements and ensuring information is provided sensitively and carefully have been highlighted as key factors in communicating bad news to people with MPM.(232)

Another consideration in communicating information to people with MPM relates to the specificity of the information. In a qualitative study consisting of focus group sessions and one-to-one interviews, caregivers of people with terminal cancer expressed frustration when the initial information they had been given (e.g. high chances of cure with treatment) later transpired to be incorrect.(304) This echoed the findings of this thesis that patients and relatives wanted certainty about the specific effects of treatment for them as an individual, and is an important consideration when communicating information to patients and relatives (as discussed in Section 6.3.8.).

Participants in TILT sought information from several different sources. This corresponds with the BLF patient survey, which revealed that most people with mesothelioma received information from their doctor or specialist nurse, but that many also considered their local patient support group or social media to be their main source of information.(302) Participants in the Mesothelioma UK survey also mentioned doing their own research on the internet and reading up about official guidance, including the Government's 2011 White Paper on improving cancer outcomes.(301, 309)

When it came to trial participation, MPM patients were knowledgeable about research studies that were available and, again, often sought information online and from other

sources.(301) Being well-informed about research may have informed the decision to participate and may have contributed to the confidence TILT participants expressed in their decision after the event. In a study of 118 people who were participating in cancer trials, Stryker et al reported that patients who scored highly on information assessments about the trial were less likely to express regret at their decision to participate.(310)

Longitudinal qualitative interviews with participants in a MPM surgical trial (the second Mesothelioma and Radical Surgery trial; MARS2) revealed that, similar to TILT, people often chose to join the trial in the hope of receiving a treatment that was not otherwise available.(172) Other motivating factors for joining MARS2 included recognition that participation brought with it an enhanced level of care and support from the research team.(172) Most MARS2 participants mentioned altruism and the desire to improve treatment options for future patients, as well as acknowledging that participating in a trial offered hope, and enabled them to take a positive approach to their illness.(172) These reasons for participating in research resonated strongly with the findings of the TILT qualitative study, and confirm that people with MPM are as motivated by altruism and the greater good as they are by potential personal gain from research.

Altruism is a recurring motive behind clinical trial participation in people with cancer. In a systematic review of 51 quantitative and qualitative studies examining oncology clinical trials, altruism was identified as a key facilitator to participation, mentioned in 25% of studies included in the review.(282) The similar “desire to help others” was cited as a motivating factor in 36% of the included studies.(282)

Potential personal gain has also been reported frequently in studies examining people's reasons for participating in research in the context of incurable cancer. "Perceived personal benefit" and "hope for a cure" were often quoted as motivating factors in oncology trials.(282) In one questionnaire study, patients with cancer alluded to limited alternative treatment options and a belief that the trial treatment was the best option available to them as their primary motivation for joining a trial.(283) Again, there are clear similarities with the motivations described by people with MPM in TILT.

TILT participants were often motivated to take part in the trial due to scientific interest and an ability to understand the rationale behind the research. This observation has not been reported previously, either in people with MPM or in people with other types of cancer. In part, this is likely to reflect the slightly restrictive study designs that were used, historically, to explore this area. Specifically, most studies relied on data collected through surveys or questionnaires. If the specific instrument did not include an option about scientific interest, then this motive would not have been detected. Recent qualitative work in MPM patients in MARS2 employed a more inductive approach to data collection, however this theme was not identified.(172) Perhaps the concept of surgically resecting a tumour was less scientifically intriguing than that of bacterial immunotherapy. Nevertheless, some participants who expressed a preference for the surgical arm in MARS2 did so on the basis that they were keen to have the tumour physically removed, whilst others talked about wanting the additive benefits of surgery

and chemotherapy, suggesting that understanding the rationale behind the treatment did contribute to people's enthusiasm to participate.(172)

Another theme that recurred between the MARS2 qualitative study and the findings from this thesis was a sense from some participants that they felt abandoned or neglected by the trial team.(172) Although most people in MARS2 felt well-supported during the trial, some commented that they would have preferred more frequent contact to reassure them that they had not been forgotten or overlooked, particularly at the point of transition from the tertiary surgical centre back to their local hospitals. This replicates the experience of one TILT participant and highlights the importance to people with MPM of regular and frequent interactions with clinical and healthcare professionals.

As the first clinical trial in MPM patients to use the TwiC design, there was no prior literature regarding its acceptability to this population. Equally, as a relatively newly described trial methodology, there was no existing data about its acceptability in other participant groups. However, other trial designs that use randomisation without consent, for example the Zelen design, have been criticised in the past for being unethical. The main criticism rests on randomisation being research activity that should not occur unless the person has explicitly consented to participate in research.(138) A similar argument has been made about the TwiC methodology in its original format (i.e. without the two-stage consent process employed in TILT).(146, 311)

The acceptability of the Zelen design and other types of randomisation without consent trials has been explored previously. McNulty et al undertook a cluster-randomised modified-Zelen trial of an educational intervention for chlamydia screening uptake in primary care.(312) GP practices were randomly allocated to implement the educational programme or not, and consent to participate was only sought from practices allocated to the intervention. Once the trial had ended, all practices were provided with information about the modified-Zelen design, their allocation and the consent process, and were invited to participate in qualitative interviews about the methodology.(313) Overall, the design was highly acceptable to those involved, with many people expressing approval for the "realistic" picture the research would generate as a result of the pragmatic design. GPs found the consent process acceptable and several people who worked in practices who had not been approached for consent described gratitude that they had not been burdened with additional governance processes when their day-to-day practice had not changed. For many people, the trial design was reminiscent of service evaluation and monitoring, and thus felt like a familiar concept. Interestingly, most people believed that the trial design should be made explicit to all participating practices once the trial had finished, and some stakeholders suggested the need for a national ethical approval process specifically for trials that involved randomisation without consent. The only perceived disadvantage of the method was the potential damage in trust between individual GP staff and the Primary Care Trusts (PCT) who had provided consent on their behalves. However, this is the usual process for cluster randomised trials based on PCTs or GP practices and did not relate to the Zelen design specifically.

The concept of randomisation without consent (or post-randomisation consent) has also been explored in lay people. In a large US study, 3739 members of the public were selected from an existing database (known to be representative of the general US population) and invited to complete an online survey about clinical trials in which the control arm did not provide consent.(314) Two separate theoretical trials were presented - a high stakes scenario of survival in leukaemia and a low-stakes scenario of blood sugar monitoring in diabetes, with two different types of wording – standard RCT language vs minimising language that emphasised the lack of change to care in the control arm. Of 2004 analysable responses, 75.4% of participants stated they would definitely or probably recommend an ethics panel to approve the study design, whilst 20.4% would probably not recommend approval and 4.2% definitely would not. Recommendation rates did not change when the trial was presented in the high or low setting, nor if it were presented using the different wording. Interestingly, people were less accepting of the design on a personal level, with only 53.2% of people stating they would be OK with being randomised to the control arm and not informed about it.

All participants in the TILT qualitative study said they were happy with the idea of control participants being blinded to the trial, as did their relatives. However, blinding had been breached in all control patients, so it was not possible to hear from someone who had participated in the trial as a control without knowing about it.

Previous qualitative work with people participating in trials has highlighted that participants can struggle with the concept of randomisation.(315-317) Qualitative interviews with people with breast cancer showed that they found it hard to understand why randomisation was necessary and disliked the idea of placebos.(318) Other studies have consistently demonstrated that people do not believe that randomisation is truly random, often believing allocation decisions are based on individual characteristics or responses to prior treatment.(315-317) People with MPM interviewed longitudinally during participation in the MARS2 trial, demonstrated variable understanding of randomisation.(172) The majority of people had a good appreciation of random allocation to the treatment arms, however several people believed that the doctors decided their treatment and others thought that the decision was based on their individual situation and responses to previous treatment. In general, TILT participants revealed similar levels of understanding to MARS2 participants, with the majority demonstrating a good understanding and acceptance of randomisation. It may be that people with MPM are more able to understand and accept the concept of randomisation, perhaps as a result of being well-informed about research in general.

6.3.10. Anxiety about the future and coping strategies: key finding 10

Key finding 10 – For people with MPM and their relatives, thoughts of the future were associated with anxiety and grief for lost opportunities. Whilst people with MPM tended to be stoical, their relatives were less accepting and often took on the role of advocate

for their family member. The specific needs of both groups should be catered for in the provision of routine clinical care.

As discussed in Section 6.3.8., being diagnosed with a terminal condition creates fundamental challenges to a person's sense of self and personal narrative.(319) Unwanted changes to a previously-imagined future are difficult to accept and are often met with a combination of grief, anger and frustration.(287) The unpredictability of what the new future holds is a source of anxiety, with patients and relatives concerned about potential symptoms and physical deterioration. In a survey of 56 people receiving palliative care for a terminal condition, 41.4% were afraid of the dying process, with 64.3% expressing concern about being in pain in future.(307) Similar fears were articulated by participants in the TILT trial. Respondents to the survey study also reported anxiety about whether their dignity would be respected (76.8%) and what they would do if they became unable to care for themselves (53.6%), although these concerns were less frequently mentioned by people with MPM.(307) People with MPM in the TILT qualitative study were more likely to focus on the practical elements of their conditions and the limitations placed on their day-to-day lives.

Some of practical factors mentioned by people with MPM were the lost opportunities and plans that were no longer possible as a result of the disease. Their relatives also described sadness about future events and experiences that would no longer happen. This theme was noted by Dr Helen Clayson in her interviews with 15 people with mesothelioma and their partners.(213) The theme, which she called "spoilt plans",

included retirement plans that had been scuppered and hoped-for holidays that had been cancelled. Grief for the loss of a future that was previously taken for granted has been reported in other cancer types and is likely a common experience across several terminal disease conditions.(320)

The tendency of people with MPM to respond to their loss with practical and stoical behaviour has been well-described in previous qualitative studies.(174, 213, 321) Similarly, the observation that relatives and carers respond differently to the emotional demands of the disease is not novel. In her work described earlier, Clayson noticed the "striking" difference between the acceptance and stoicism demonstrated by men with the disease and the "passionate anger" their wives displayed on their behalves.(174, 213) As described in this thesis, relatives of people with mesothelioma felt they had to fight on behalf of their loved one, either because their relative was too accepting of the situation or was too ill to fight for themselves.(174)

Advocacy often focussed on the medical care received by people with mesothelioma. In the Mesothelioma UK patient survey, relatives sometimes described dissatisfaction with the care their partners received, as did family members in Clayson's interviews.(213, 301) The dissatisfaction often related to organisational issues (as mentioned by Caroline in the TILT qualitative interviews) and a perception that medical interventions and investigations were not occurring in a timely fashion.(308) This pattern was not unique to people with mesothelioma, as Gribich and colleagues demonstrated in their interviews and focus group sessions with care-givers and bereaved relatives of people

with other terminal cancers.(304) They found a similar theme of relatives advocating on behalf of their unwell family member, particularly if they felt healthcare staff were not listening to the patient's needs.

The role of advocate was associated with (and potentially driven by) a heavy emotional burden for carers. This thesis demonstrated that relatives were often living with an inescapable awareness of their loved one's imminent mortality, often listening out to check that they were still alive. Whilst this particular anxiety has not been described in the mesothelioma literature before, one Italian questionnaire study noted that carers of people with MPM were more likely to report intrusive or disabling fear compared to people who were not carers.(322)

In less specific terms, the high emotional burden experienced by carers of people mesothelioma has been highlighted by multiple qualitative studies.(213, 214, 321, 323, 324) The change in role from partner to care-giver/nurse has been described as stressful and relatives often reported tiredness, sleep disturbance and feelings of helplessness as a result.(214, 322-324) Carers often neglected their own health, and in one study, a number of carers for people with mesothelioma disclosed that they had started smoking again due to the stress of being a carer.(213)

Relatives faced additional emotional challenges that were not shared with their partners. Coping with their relative's death was one such difficulty, as was managing the legal processes and post-mortem requirements that accompanied their

bereavement.(174, 213, 321) This topic was not addressed during this thesis, although several relatives referred to what their life might look like after their partner had died, either directly or indirectly.

Clearly the needs of carers are significant and appear to be slightly different from those of people with MPM. Fortunately, there are an increasing number of resources available to provide this, both in the UK and further afield. Charitable organisations such as Macmillan and Mesothelioma UK have provided funding for mesothelioma specialist nurses who provide a consistent point of contact and supportive option for patients and relatives affected by mesothelioma. In some older qualitative studies, carers reported feeling unsupported by healthcare workers,(323, 324) however more recent data describe a predominantly positive picture regarding the impact of dedicated mesothelioma nursing teams.(232, 301, 308) Carers appreciated the regular close relationship that they developed with the specialist nurse and recognised the benefit of the nurse's experience dealing with other people with mesothelioma, which enabled them to understand many of the nuances and complexities associated with this specific disease.(308)

Patient support groups were mentioned by several patients and carers in TILT and were seen as a useful place to seek information and emotional support. The value of support groups in mesothelioma has been demonstrated elsewhere,(303) and they are an increasingly popular venture, often run by the local mesothelioma specialist nurse. Importantly, one TILT qualitative participant commented on a negative aspect of the

support group, that it highlighted the high mortality associated with the disease as group members inevitably died. She said the support group sometimes felt like people were “sitting around waiting to die”. Nonetheless, that person often attended the support group, even when her husband was unable to, and she maintained that she found it helpful and derived support from it. Patients and carers who did not have access to a support group stated that they would like to be able to attend one in their responses to the Mesothelioma UK survey.(301) In general, it seems that patient and carer support groups are a positive resource, and one that all people with mesothelioma should be able to access, even if they choose not to attend.

6.4. Strengths and limitations of the research

A major strength of this research was the use of mixed methods to tackle different aspects of the research question. By employing a quantitative observational methodology alongside a clinical trial with embedded qualitative interviews, the research has provided a multi-faceted perspective on the subject of intra-pleural bacterial immunotherapy in MPM and yielded broader and richer results than any single approach would have.

The interplay between the qualitative study and the clinical trial was the most beneficial. Qualitative interviews, analysed contemporaneously, enabled modifications to be made to the trial protocol to increase acceptability and improve the experience of subsequent participants. Qualitative interviews with later participants allowed the changes to be reviewed, to determine whether they had improved the trial or not, with further modifications made to the protocol if required.

The findings of the quantitative and qualitative study complimented each other, with each element providing information of a different facet of the overall project. It was useful to learn, from the qualitative study, that the TwiC design was acceptable, even though the trial demonstrated it not to be feasible to use in this context. Chapter 1 described the different approaches to mixed methods research and a diagram was provided to represent the relationship between the qualitative study and the feasibility trial. The diagram is recreated below (Figure 6.2) with annotation describing the specific way the two methods interacted to inform the findings.

6.4.1. Systematic review

A strength of the systematic review was the robust methodology, conducted in accordance with the Cochrane Handbook for Systematic Reviews. The search strategy was thorough and undertaken with the support of an information scientist from the University of York. Study selection, data extraction and risk of bias assessment were undertaken by two independent reviewers, with any discordance resolved by discussion.

Unfortunately, five papers that were deemed eligible for inclusion were not available for full text review. Multiple attempts were made to source these manuscripts, including contacting the British Library and personal correspondence (written and email) with the relevant authors, however to no avail. Whilst this is perhaps unsurprising given almost 3 decades had passed since publication in some cases, the missing papers may have introduced bias and affected the findings of the review.

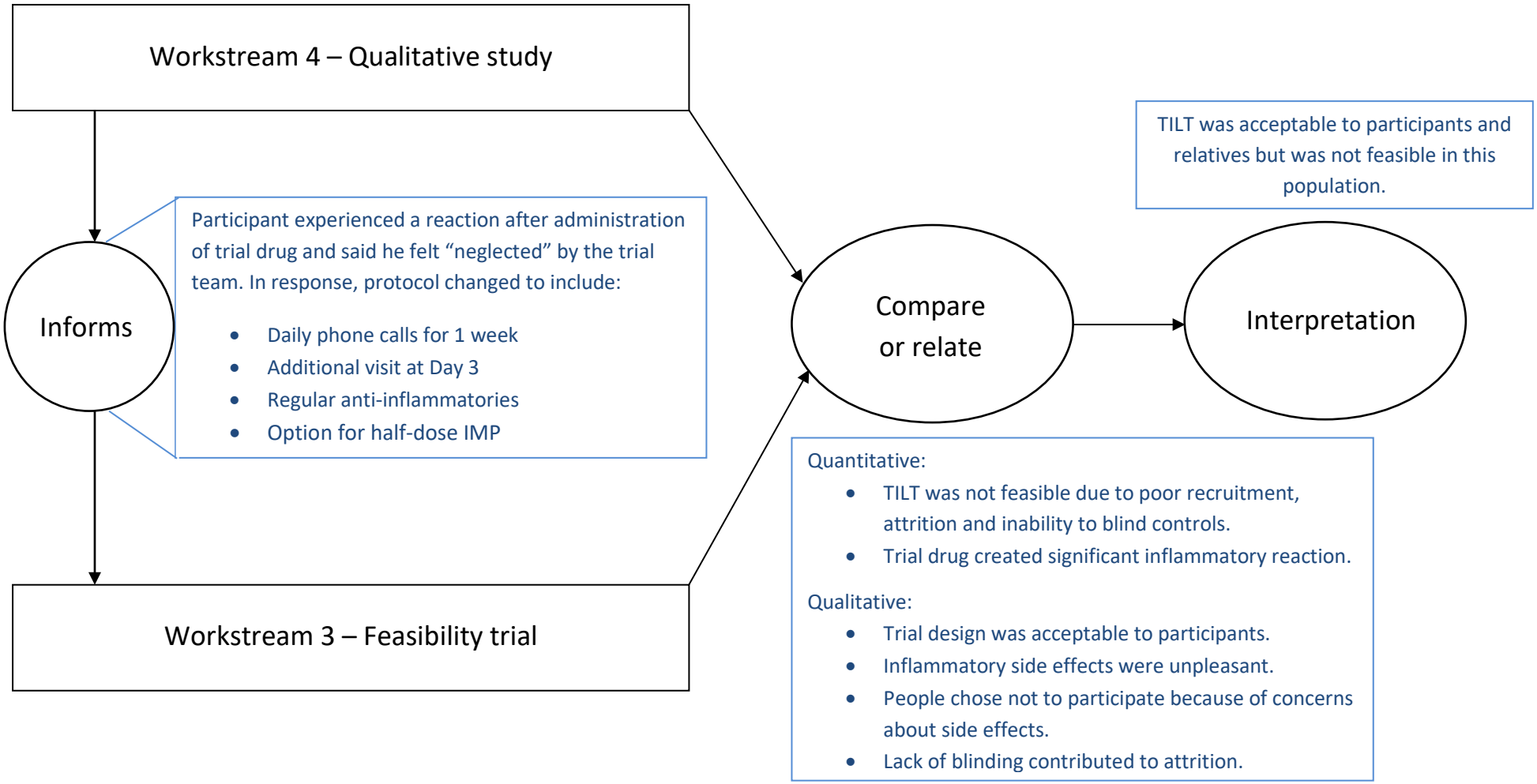


Figure 6.2 Schema of a parallel, concurrent, interactive model of mixed methods research with subsequent convergence, annotated to demonstrate application to this thesis.

Although not a limitation of the systematic review itself, the quality of the literature available for inclusion was poor. As described in Chapter 2, approximately half of the included studies were non-randomised, observational studies, at high risk of confounding and selection bias. Few studies were designed with survival as a primary outcome, and consequently reporting of survival endpoints was imperfect. Measures of variance were rarely provided, which prevented interpretation of survival estimates. Additionally, survival outcomes were rarely adjusted for other variables, raising the very high risk of confounding due to patient or tumour characteristics.

There was a high degree of heterogeneity between the papers included in the systematic review. Not only is MPE a heterogeneous disease, caused by multiple different pathologies with different prognoses, but there are also several different bacterial products that have been studied in clinical trials, at different doses and regimens. As previously discussed, this heterogeneity made synthesis of study findings difficult, particularly in terms of evaluating the overall effect of any specific bacterial products in a single disease process.

6.4.2. Population-based cohort

The population-cohort study had several strengths. The use of data from a resource with universal coverage of activity in NHS hospitals across England minimised selection bias. Similarly, the use of standardised coding within HES, using ICD-10 and OPCS-4, ensured that identification of study participants was comprehensive. Compared with national cancer registry data from the Office of National Statistics, our study identified between

94.3% and 100% of patients diagnosed with mesothelioma in England each year.(325) Similarly, the number of deaths recorded for the years 2006 to 2014 in the study represented 92% to 98% of the total mesothelioma deaths recorded by the Health and Safety Executive in England for those years.(33) Finally, the 1-year survival rate for patients diagnosed in 2014 was comparable to that reported in the National Mesothelioma Audit (38.8% *vs* 43.1%) as was the proportion of patients diagnosed after 2008 who received chemotherapy (36.0% *vs* 36.5%).(38) It is likely, therefore, that the study population was a reliable representation of the mesothelioma population in England during this period.

Unfortunately, there is less certainty regarding identification of pleural infection. The incidence of pleural infection in patients with mesothelioma has not been reported previously, and so it was impossible to know whether case identification was comprehensive. Since the same method of identifying cases was used, it was hoped that detection of pleural infection was as sensitive as it was for mesothelioma. It could be argued that mesothelioma was more likely to be correctly coded than pleural infection, given it is a legally notifiable disease. However, the lack of alternative data sources to validate pleural infection rates against made it impossible to evaluate the sensitivity of pleural infection identification within the cohort.

The incidence of pleural infection in the general population is 6-22 per 100,000 - much lower than the incidence observed in mesothelioma patients in this study.(326, 327) Mesothelioma patients are at higher risk of pleural infection than the general public, as

they undergo multiple pleural interventions, each carrying a risk of infective complications. It may be that the higher incidence observed here is a reflection of that risk. An alternative possibility is that pleural infection was a misdiagnosis in a proportion of people with mesothelioma. As part of the disease process, someone with mesothelioma could present with fevers and sweats, alongside a loculated pleural effusion, which may well have a low pH. Several of these features would also be found in pleural infection, so misdiagnosis, particularly at first presentation, is conceivable. However, patients were only entered into the cohort study once mesothelioma had been diagnosed and episodes of pleural infection had to occur after the diagnosis had been made. Diagnostic confusion was less likely to occur once mesothelioma had been confirmed, and therefore, misdiagnosis is unlikely to explain the increased rates of pleural infection seen.

Another strength of the study was the statistical analysis plan. Splitting follow up at infection and at 30 days reduced the risk of immortal-time bias affecting the results, i.e. patients with pleural infection had to have lived long enough to have developed pleural infection. Handling pleural infection (as well as chemotherapy and thoracic surgery) as time-varying covariable removed this potential bias.

The cohort study was affected by a major limitation, namely the lack of information available about potential confounding variables. Specifically, patients' performance status and tumour histological sub-type were not available. These factors are known to be prognostic in mesothelioma and could plausibly affect the risk of acquiring pleural

infection as well, thus creating confounding.(1, 44) For example, it is possible that pleural infection was more likely in patients with worse performance status, and the higher mortality related to their performance status rather than infection. To adjust for this, the variable "comorbidities" was created, as a surrogate marker for performance status. This approach was imperfect, though, as performance status is a global measure of functional status that encompasses more than just co-existent medical conditions. Nonetheless, it was reassuring that the mortality hazard did not change greatly when adjusted for comorbidities and age, the two factors most likely to reflect overall performance status.

HES also lacked data on the causative organisms driving pleural infection. As previously described, different bacterial species elicit differing immunological responses, and it would have been useful to be able to analyse the effects of different infective aetiologies on survival.(242, 243) Additionally, certain bacterial species secrete virulence factors known as superantigens, which bypass classic antigen-binding pathways and induce dramatic inflammatory responses, including polyclonal T cell proliferation and activation, and cytokine storm.(328) It is possible that evaluating all aetiologies of pleural infection *en masse* may have masked a true effect related to one single organism or species (e.g. staphylococcal infections only).

Where HES collected information on a variable, missing data were rare. However, it was noted that patients with missing socioeconomic data had dramatically better survival outcomes. Whilst this could represent a genuine result, it is more likely that some of

these patients had missing data for other variables, including date of death. This would have resulted in these patients appearing to live much longer. Post-hoc investigation revealed that patients in these groups were more likely to have been right-censored than other groups, supporting this theory. However, patient numbers were small, and a sensitivity analysis omitting these patients resulted in near-identical results to the primary analysis.

6.4.3. TILT trial

A strength of TILT was that it faithfully recreated the processes required to undertake a TwiC of intra-pleural immunotherapy in MPM. Like all well-executed feasibility studies, this enabled identification of potential challenges that could affect a full-scale trial, saving significant time and money compared to a definitive trial. Because TILT replicated the exact methodology of a potential full-scale trial, the difficulties encountered during trial delivery would be equally likely to affect the full-scale trial. Based on the results of TILT, a full-scale trial of intra-pleural bacterial immunotherapy should not be based on the TwiC design and would require a large number of recruiting centres and/or an extended recruitment period to ensure a suitable number of participants were enrolled.

Another strength of TILT was the qualitative interviews embedded within the trial design. Because these were analysed contemporaneously, the research team were able to respond to themes as they were identified and modify the trial design to optimise acceptability. An example of this was the alteration to the trial follow up regimen after

the first participant experienced an SAE. A theme arose from his and his wife's interviews about feeling "abandoned" and "isolated" in the days after IMP administration. This was discussed at the next Trial Steering Committee meeting and the protocol was amended to add daily phone calls for a week after IMP administration and an extra trial visit at day 3. Subsequent participants commented on feeling well supported and looked after by the trial team.

The changes made to the trial processes in response to the qualitative findings were relatively easy to make but had an important impact on participants' experiences. The responsiveness afforded by using an integrated mixed-methods approach meant that the final processes that we used in the trial were the most acceptable they could be to participants and their relatives. Although other elements of TILT rendered a full-scale trial non-feasible, the assimilation of qualitative outcomes into the trial design maximised the acceptability of the trial and we can be as confident as possible that lack of acceptability was not a key barrier to trial delivery. Additionally, the qualitative findings are likely to inform the design of future trials in MPM patients, even if the TwiC methodology is not utilised.

A final strength of the trial was the use of validated measures for all secondary outcome measures. Although, as a feasibility trial, TILT was powered to detect a pre-determined feasibility outcome (attrition) and not to evaluate efficacy outcomes, use of these measures would strengthen any future full-scale trial.

There is, however, a recognised limitation to the performance of cross-sectional imaging in the evaluation of MPM. CT scans have been shown to have a low sensitivity for detecting MPM, particularly in early stage disease.(329) Additionally, evaluating radiological TNM (Tumour, Node, Metastases) stage is difficult on CT, with a high degree of inter-observer variability, particularly relating to subtle changes such as invasion of the diaphragm.(330) Magnetic resonance imaging (MRI) is more sensitive for detecting MPM with minimal pleural thickening and for assessing invasion of soft tissue, however assessment of response remains problematic.(331) The circumferential growth pattern of MPM makes 3-dimensional assessment more important but also more challenging than for more commonplace rounded tumours. mRECIST relies on multiple measurements of tumour thickness taken at different levels and positions within the chest cavity to ascertain whether progression has occurred, with disease progression defined as an increase in the sum of these measurements of 20% or more.(208) However, this approach is vulnerable to inconsistency in tumour measurement as well as in choice of site to measure.(332) Additionally, a tumour could become significantly bulkier in all dimensions without a 20% increase in the areas where the specific measurements were taken. Finally, there is poor correlation between TNM stage and mRECIST as serial markers of disease status. It is perfectly possible for a tumour to be upstaged on TNM without meeting the mRECIST criteria for disease progression, for example via new invasion of the diaphragm.

Tumour volume, assessed on CT or MRI, provides a more accurate evaluation of MPM tumour size at diagnosis and evolution over time. Volumetry has been performed in

MPM in several academic centres and shown to be reliable and consistent, if time-consuming.(333) The development of artificial intelligence software (AI) to perform automated 3-dimensional evaluation of MPM tumours is likely to have a dramatic impact on the radiographic assessment on MPM, and should be included in any future full-scale trial.

Another consideration for a full-scale trial relates to the open-label nature of both trial arms. Although with the TwiC design, the intention is for controls to be blinded, this was not possible in the TILT population. This could have introduced assessment bias, particularly in the completion of patient-reported outcome measures – data that are inherently subjective. People who received an IMP may have been more aware of symptoms and therefore more likely to score them highly. Alternatively, participants in the control arm may have been so disappointed not to receive an IMP that it impacted on their quality of life. The conclusion not to proceed to a full-scale TwiC and to consider a modified approach of a classical, double blind RCT embedded in a cohort removes this limitation.

The longer survival observed in TILT participants compared to national figures highlights a frequent issue affecting MPM trials, that of selection bias. The fact that both control participants and people who received an IMP lived longer than expected meant that the positive outcome could not be credited to IMP efficacy. Nor was it likely that the act of participating in the trial conferred a survival benefit. Instead, it is probable that the people who participated in the trial had a better prognosis at the outset and this was

reflected in their enhanced survival. The enrolment of a skewed population to the trial may be due to the eligibility requirements, e.g. good performance status, or may be a result of healthier people being more likely to participate in a trial. Whilst this bias often cannot be avoided, it should be acknowledged. This finding also serves to emphasise the importance of having RCT data to evaluate any intervention: had TILT been a single-arm study of OK432 or BCG, the longer survival could have been misattributed to the IMP. Having a control population with a similarly long survival clearly signified that this outcome was affected by bias.

Another bias that was likely to have affected TILT (and contributed to the selection bias described above) is survivorship bias. Participants enrolled in TILT were not required to be newly diagnosed, indeed only two people were randomised within a month of receiving their diagnosis. The remaining participants were enrolled between 3 months and 30 months after diagnosis. MPM is a heterogeneous disease and whilst the prognosis is poor for most, there is a recognised sub-group of long survivors who have very indolent disease.(1, 44) The participant who joined TILT 30 months after his diagnosis had already outlived the predicted 12 month life-expectancy for MPM by a substantial margin and was, therefore, almost certain to be a "long survivor". It was not a surprise, therefore, that he remained alive 15 months later when survival was censored. The receipt of an IMP in the latter third of his overall recorded survival could not possibly explain his prolonged survival prior to joining the trial, but nor should it be assumed to be the cause of ongoing survival. Both phenomena are most probably attributable to his underlying disease process.

Survivorship bias is a particular risk in post-front line therapy trials. By definition, participants must have survived long enough to complete first-line therapy, which precludes patients with more aggressive disease phenotypes. This is a potential explanation for the recurrent pattern of positive single-arm phase II trials being followed by negative phase III RCTs in MPM.(50, 51)

As well as affecting outcomes, the selection and survivorship bias that affected TILT would limit the external validity of full-scale trial using this methodology. The trial population was not representative of the UK MPM population and this is also likely to be the case for a subsequent full-scale trial. Therefore, the results of a full-scale trial would not be generalisable to the wider patient group. This undermined one of the fundamental aims of TILT, which was to be a pragmatic trial that closely resembled real-world care and had high external validity.

6.4.4. Qualitative study

Embedding qualitative research within the TILT trial allowed rich and holistic data to be collected about the acceptability of the trial design, augmenting the quantitative feasibility data. In addition, the qualitative interviews provided a detailed depiction of the attitudes, expectations and experiences of people with MPM and their relatives in regard to both the trial and MPM. The inductive and flexible nature of qualitative research enabled identification of previously unreported themes (e.g. certainty and risk communication) and provided the space to explore these themes with subsequent participants.

6.4.4.1. Credibility

Several themes identified in the qualitative study have been described in previous work relating to the experience of living with MPM. The theme of physicality and the value placed on health and strength was reported by Dr Clayson in interviews with men with mesothelioma and focus group sessions with their wives.(174) She described the deterioration in body-image as damaging to men's sense of self, as their prior fitness had been a major asset during physically demanding jobs. She also noted the stoicism and acceptance with which men responded to the diagnosis of mesothelioma, and contrasted this with the responses of bereaved wives, which were characterised by "intense passion, anger and fierce determination" to fight on behalf of their husbands. The TILT qualitative study noted similarly contrasting responses between the two groups and this replication of previous qualitative outcomes increased the credibility of other findings from this study.

6.4.4.2. Sample size & information power

The purposive sampling strategy was robust, with the different aspects of trial participation reflected in the qualitative data. Specifically, people who participated in both active and control arms were interviewed, and the views of participants who declined to participate were also represented. Based on Malterud's theory, the specificity of the TILT qualitative study population, the narrow study objective and the quality of the dialogue meant that the sample size had high information power to address the study aim.(231) Certainly the data collected was interesting, insightful and appeared trustworthy, given the areas of consistency with previous MPM qualitative

work. The aim of the study was addressed satisfactorily and several additional findings were uncovered that had relevance to current and future clinical and academic work in MPM.

Notwithstanding the high information power of the sample, it must be acknowledged that the qualitative sample size was vulnerable to being influenced by recruitment to TILT. Had interviews been limited to TILT participants and their immediate family members, the fact that TILT underrecruited could have limited the qualitative findings. However, the addition of snowball sampling to enable additional relatives, friends and carers to be invited to interview overcame this potential limitation. Ultimately, snowball sampling was not required and, aside from the wife and daughter of one participant, only one relative of each TILT participant was interviewed for the qualitative study. However, the option to recruit additional relatives and friends if a larger sample size were needed was a strength of the study design.

6.4.4.3. Transferability

Unfortunately, not everyone who was invited to participate in the qualitative study agreed. Of the trial participants, two did not participate in an interview; in both cases this was because the person was nearing the end of their life and was too unwell. One lady had actually agreed to take part in the qualitative study but deteriorated rapidly and died before the interview took place. This meant that the study did not include any experiences of people in the terminal phase of their disease. The daughter-in-law of one man who was nearing the end of his life participated in the study and provided an

account of his experience from her perspective. The husband of the lady who died prior to interview was invited to participate in the study but he did not respond to the invitation. He was the only relative to be bereaved during the study.

The qualitative findings may not reflect the views of people who are in the final stages of MPM, therefore. These people may have had specific experiences and perspectives that were not shared or reported by people who were not in the terminal phase. For example, people who were dying from MPM may have felt the trial processes to be more burdensome, or they and their relatives may have felt resentful that the limited time they had left together was being spent on the research trial. Alternatively, people may have been comforted by the idea that they were contributing to something with long-lasting impact, and the research may have given them a sense of purpose during their final days. All of these views have been reported previously in interviews with patients dying of other cancers and their bereaved carers.(334, 335)

Clearly, the experiences of people participating in research during the terminal stages of MPM are important and interviews with people in this situation would provide valuable information. However, research is difficult to conduct in this population. Potential participants are likely to have reduced mobility, low energy levels, poor concentration, and active symptoms such as breathlessness and pain. These create practical and ethical barriers to participation in research.

Despite the absence of people in the terminal phase of MPM, many of the experiences reported in the qualitative interviews will have been shared by others with MPM, whatever stage of the disease they are in. The 'biographical disruption' described by Bury was apparent in the narratives of TILT participants and will have been experienced by many people with MPM.(287, 319) Similarly, the thirst for information and desire for certainty are unlikely to be unique to interviewed participants. Therefore, although the data reported here did not specifically include people in the terminal stages of MPM, many of the findings should resonate with their experiences, nonetheless.

The study sample was entirely made up of white British participants in late middle age or older. TILT trial participants who were interviewed were all male. Although this sample may not be representative of the general population, it is a typical reflection of the UK population of people with MPM.(38) Therefore, the findings are likely to be transferable to the wider UK MPM community. That said, people with MPM from other racial, ethnic and cultural backgrounds may describe different experiences of living with MPM and of participating in research, as may women with MPM. The views and experiences of these groups of people should not be ignored simply because they represent a minority of the MPM population. Indeed, their minority status makes a stronger case for understanding their experiences to obtain a full picture of the experience of MPM across all patient groups.

6.4.4.4. Reflexivity

Reflexivity is an important element of all qualitative research, and a poor appreciation of the impact of the researcher and their individual characteristics on data collection and analysis can undermine the credibility of the results.(336) In the TILT qualitative study, all interviews took place between participants and myself. I kept a diary of reflections during the study to capture my experience of the process and reflect on my positionality within the interviews and data analysis, as advised in several qualitative method guides.(228, 337) There were three areas where my personal experience, role and background intersected with qualitative study processes. These areas are described in turn below and their potential effect on the work considered.

The first reflexivity point related to my role as a MPM clinician and PI for the TILT trial. I had met all of the qualitative participants at least once prior to their interviews and all were aware of my position within the trial. In her article on qualitative research, Prof Nicky Britten stated that clinicians should not interview their patients, as participants may be more likely to say what they think their doctor wants to hear.(240) However, she goes on to recommend that if this situation cannot be avoided, patients should be given permission to speak freely and should not be corrected if they express a view or opinion that the doctor disagrees with. This was the approach I adopted.

However, despite encouraging participants to speak openly and honestly about their experiences, it must be considered that my clinical and research roles may have influenced participants' responses during the interviews. Specifically, it is perhaps not a surprise that the majority of people reported positive experiences of the trial and made

few suggestions for improvement or change, given that they knew the trial had been designed by the person sat in front of them. To overcome this, interviews were presented as a collaborative effort to improve future research for other people with MPM, rather than a specific critique of TILT. Additionally, I approached the interviews with a humble and receptive manner, and all comments, positive or negative, were received with interest and encouragement. This approach appeared to be successful, as two participants were particularly forthcoming and spoke at length about their perceived criticisms of the trial. This suggested that my manner encouraged negative as well as positive feedback.

My role as a clinician with MPM experience and pre-existing clinical relationships with many of the participants may have had some beneficial impact on the study. For example, I have received extensive training in communication skills during my medical training and have been involved in difficult conversations e.g. breaking bad news and discussing end of life issues, on a regular basis since qualifying as a doctor. These experiences were extremely useful when conducting interviews and enabled me to discuss potentially upsetting issues in a sympathetic and sensitive manner. Additionally, the pre-existing clinical relationship between several participants and me meant that dialogue was potentially easier because a level of trust and mutual respect had already been established.

The second important area of reflexivity related to my inexperience as a qualitative researcher. Reading my reflections diary, there was a clear learning curve with regard to

interview technique, specifically how comfortable I felt with silence and allowing people time to formulate their own thoughts. Reflecting on this behaviour led me to William Whyte's guidance on conducting qualitative interviews, which included techniques such as reflecting back remarks made by the participant and asking for expansion on comments of interest.(338) Adopting these methods strengthened my interview skills and, listening to the audio-recordings of the interviews, it is clear by the third interview that my practice was much improved.

Finally, I became increasingly aware during the qualitative study that interviews with female relatives were longer, richer and more open than the interviews with male participants. In part, this may have been a reflection of the different behaviours of the two groups, i.e. that men tended to be stoical and down-play events, whilst their wives and daughters were more vocal and likely to advocate on their behalves. It must be considered, however, that my own gender may have been a factor in encouraging female participants to talk freely. The corollary is that men may have felt less able to open up to me, as a woman, although based on discussions in PPI groups and the overall experience of working with men with MPM, it seems unlikely that male participants would have been any more forthcoming with a male interviewer.

Another possible explanation for the quality of data obtained from interviews with female relatives relates to my own experience of bereavement. Prior to the study I was aware that I felt great sympathy for people with MPM and their relatives, but the additional empathy I had for relatives' impending bereavement became evident as the

study progressed. I suspect that this empathy contributed positively to interviews with relatives. This phenomenon has been described previously, by Dr Jenny Bozenski, who interviewed 12 clinical psychologists about the experience of bereavement on their work.(339) They described increased empathy towards clients in the aftermath of bereavement and greater sensitivity to their grief. In many cases this enhanced therapeutic interactions, as it is likely to have done in the TILT qualitative interviews.

6.4.5. Co-production and patient & public involvement

The work undertaken in this thesis was planned and designed in close collaboration with patients and the public during dedicated co-production meetings and patient and public involvement (PPI) group sessions.(340) This ensured that the content and overall aim of the research was consistent with the priorities and values of the people at the heart of the thesis, i.e. people with MPM. The close involvement of the dedicated PPI group, who reviewed the protocols, consent forms and all patient-related resources for TILT and the qualitative study, was likely a crucial factor in the overall acceptability of the trial to participants and relatives.

The suggestions made by the PPI group and the changes made to the study protocols following their recommendations have been described in the relevant sections. Briefly, the trial follow-up regimen, the choice of patient-reported outcome measures, the decision to include friends as well as family in the qualitative study, the appropriateness of approaching bereaved relatives and the best manner to do this, the choice of

interviews over focus groups for people with MPM and the qualitative topic guide were all strongly informed by the PPI group.

The opportunity for mutual learning was evident during the PPI sessions. The academics and clinicians enjoyed meeting patients outside the usual hospital setting and felt it allowed a more holistic view of patients as “real people”, each with their own knowledge, skills and experience to bring to the trial. Participants in the PPI groups, which included people with MPM, carers of people with MPM and bereaved relatives of people who had died from MPM, were interested to learn about the processes that take place ‘behind the scenes’ in academic research, and said how much they appreciated the opportunity to contribute to the process. Overall, everyone involved in the PPI work experienced a sense of partnership, with a shared purpose and joint commitment to try & improve knowledge and treatment in MPM.

There are two rationales for including PPI input in the design and implementation of clinical research. The first is a moral argument, i.e. the people most affected by the condition being studied should be involved in deciding what research is done in the area, and how. This argument stems from the accepted premise that it is not acceptable to research *to*, *on* or *about* people, rather it should be done *with* or *by* them.(341) The second argument is consequentialist and relates to the fact that PPI can improve the quality, efficiency and dissemination of clinical trials.(342) Both arguments are compelling and will appeal to different stakeholders, for example, funders may be more interested in the consequentialist logic, whilst patient charities and advocacy groups will

prefer the moral reasoning. Either way, there are indisputable benefits from PPI, which make non-inclusion difficult to justify.

There are challenges in PPI work, however, including the practical demands on participants.(343) For people with MPM who may have troublesome symptoms, this should not be underestimated. Additionally there is an emotional burden of re-visiting issues relating to their illness (which men with MPM were often reluctant to do based on the findings of our qualitative work).(343) Finally, and of particular pertinence to people with MPM, there is the issue that contributing to PPI and the types of discussions held during PPI meetings may serve as an unwelcome reminder to patients about the poor prognosis of MPM and the lack of treatment options available. Mesothelioma researchers have described patients and relatives becoming upset or even leaving meetings where research is being discussed, as a result of the sheer volume of negative information presented.(260) The authors of that report suggest a novel approach to mesothelioma PPI analogous to a speed-dating event, where patients and carers rotate in groups around stations or tables where a researcher is sat. Discussions can take place on a more personal level, with information exchange tailored to the people in each group. A similar approach has been trialled at one of the Bristol patient and carer update days, with positive feedback from all involved. PPI for future MPM trials will adopt a similar approach.

6.5. Future research

There remains uncertainty regarding the role of intra-pleural bacterial products as immunotherapeutic agents in MPM. The systematic review highlighted the need for well-designed, suitably powered, RCTs to determine whether these agents prolong survival. Such a trial would require certain methodological decisions to be made upfront and the finding of this thesis may inform those decisions.

6.5.1. Choice of bacterial agent

The systematic review did not identify any single bacterial agent that was likely to be more effective in the treatment of malignant pleural disease. However, certain difficulties encountered during the set-up of the TILT trial could guide the choice of agent for future trials. Unfortunately, several bacterial agents are no longer commercially available, despite initially promising clinical trial data. Unavailable agents include *Lactobacillus casei, Nocardia rubra* and *Corynebacterium parvum*.

OK432 was obtained for the TILT trial, albeit with some logistical difficulty and at considerable expense. Although an established procurement pathway has now been established and a reliable importation company identified, the costs associated with obtaining OK432 remain high, with no expectation of bulk savings if a larger trial were planned. It should also be noted that OK432 failed to demonstrate any positive effect on survival in all previous trials that applied it in pleural malignancy.

The other bacterial agent studied was BCG, a drug that has an established role in bladder cancer and is therefore easily obtainable through NHS procurement pathways. In the systematic review, BCG was associated with a survival benefit in both studies that employed it, although they were non-randomised and at high risk of bias in several domains. These findings are in keeping, however, with the established anti-neoplastic effect of intra-vesical BCG in bladder cancer.(108-113) BCG also exerts a cytotoxic effect in melanoma, inducing tumour regression and significant prolongation of survival following intra-lesional administration.(115) The exact mechanism of action is unknown, but is likely to involve activation of CD4+ and CD8+ T lymphocytes and release of cytokines, such as interferon-gamma and tumour necrosis factor.(105, 106, 344, 345) The scientific rationale, pre-clinical data and clinical evidence is strongest, therefore, for BCG, and it certainly induced significant inflammatory responses in patients who received it in the TILT trial.

Further information is needed regarding the frequency and severity of BCG-related inflammatory responses in people with MPM. There is an interesting question to be answered regarding immunological memory to *M. Bovis* and whether people who react strongly to tuberculin skin testing are more likely to experience severe reactions to intra-pleural BCG. Given the priorities of people with MPM, as described in this thesis, the risk of potential reactions following intra-pleural BCG would need to be balanced against its potential efficacy (and clearly stated in the PIS) if a future full-scale trial were planned. Fear of side effects may limit recruitment to a trial and, ultimately, BCG treatment may not be accepted by MPM patients, even if efficacy were demonstrated.

6.5.2. Participant recruitment

If a full-scale trial of intra-pleural bacteria in MPM were planned, the challenge of recruitment would need to be addressed. It is now clear that the population of people who would be eligible for the trial is smaller than was anticipated at the beginning of this PhD. One option to overcome this would be to increase the number of recruiting sites and establish participant identification centres (PIC) to refer people into the trial from distant hospitals. However, given the small number of cases of MPM seen in most hospitals, this is unlikely to radically increase numbers. Extending the recruitment window would be another option, but this would be associated with higher costs and resource requirements. Additionally, there is an element of urgency in undertaking this work in order to find an effective treatment before MPM incidence falls to such a degree that the treatment is no longer required. A trial period of several years is not ideal in this context.

An alternative approach would be to relax the inclusion criteria. The factor that most frequently rendered people ineligible for TILT was the lack of an IPC, or absence of a pleural effusion. An ongoing trial of an intra-pleural oncolytic adenovirus has attempted to avoid this issue by including the option for patients to have an IPC inserted surgically, in the absence of a pleural effusion (NCT03710876). However, given the increasing age of the MPM population and associated co-morbidities, it seems likely that a reasonable proportion of people will be unsuitable for surgical implantation of an IPC.

The presence of non-expandable lung and loculations in the pleural cavity must remain as exclusion criteria for two reasons. Firstly, in order to stimulate an immune response, the bacterial agent must be able to come into contact with the pleura, rather than simply gather in a discrete locule. Secondly, we have shown that intra-pleural bacterial agents are highly inflammatory and, if delivered to patients with non-expandable lung, are likely to result in a complex, multi-loculated effusion which could cause symptoms but could not be drained. This would clearly be unacceptable.

Another eligibility criterion that cannot be changed is that of no concurrent chemotherapy. Whilst some clinicians (including us) may feel braver about administering inactivated and killed bacteria alongside immunosuppressant medication such as chemotherapy, the most promising bacterial agent, BCG, is a live-attenuated bacteria, and would be carry a high risk of uncontrolled infection if administered in the context of chemotherapy. The phenomenon of disseminated BCG-osis that has been reported after intra-vesical use of BCG in bladder cancer supports our concerns in this regard.(346, 347)

A final consideration regarding the feasibility of a future full-scale trial of intra-pleural bacterial immunotherapy is the evolving treatment landscape and increasing number of competing clinical trials in MPM. As the evidence grows for the use of systemic immunotherapy agents in MPM, more patients are keen to receive them, whether as part of routine clinical care (depending on the formal results of CHECKMATE-743), in a clinical trial or off-label, financed by compensation packages. It seems probable that

over the next few years, patients will increasingly elect to pursue one of these treatments, rather than receive an unproven intrapleural bacterial agent. Additionally, it is important to note that most of the clinical trials of checkpoint inhibitors excluded people who have previously received immunotherapy. There is an ethical dilemma about recruiting patients to a clinical trial that may preclude them from receiving an effective treatment at a later date.

6.5.3. Trial methodology

The work described in this thesis has shown that the TwiC methodology is not feasible for future trials in the MPM population, due to an inability to maintain blinding of the control arm and attrition from the intervention arm after randomisation. However, elements of the design remain attractive and of potential benefit to future MPM trials, specifically the possibility to increase recruitment efficiency by screening within a cohort and the option to collect long-term outcome data on both trial participants and people who decline trials.

On this basis, I propose a modified TwiC methodology for MPM, consisting of a standard double-blinded, placebo-controlled RCT embedded within the ASSESS-meso cohort. Screening for trial eligibility could take place at regular cohort assessment visits, and if a person is found to be eligible, they are approached in the usual fashion and standard RCT process followed. With this approach, all ASSESS-meso centres could function as PICs, with patients being offered the option to travel to one of the main trial sites if they were interested in the trial. Using a double-blind, placebo-controlled design, these

patients would be less likely to withdraw from the study after randomisation. On completing the trial at the trial centre, they could return to their local centre for ongoing data collection as part of ASSESS-meso. In this way, the benefits of the TwiC are maintained, whilst the challenges encountered during TILT are eliminated.

6.5.4. Qualitative studies

The qualitative work undertaken as part of this thesis highlighted several areas of interest for future research studies. Most pressingly there is a need to understand more about perception of risk in people with MPM and the most effective way of communicating uncertainty to patients, in both the clinical trial setting and in the context of clinical care. A reasonable starting place for this work would be to review existing clinical documents that discuss benefits and risk, e.g. patient information sheets about biopsies and thoracoscopy, and explore how they are perceived and interpreted by patients and their relatives. This could be done using a cognitive interviewing approach.(348) This is a technique that is usually applied to the development of questionnaires or surveys but could equally be applied to patient information leaflets. Participants are encouraged to think aloud as they read the document, whilst an interviewer may ask additional questions to enable initial thoughts to be expanded upon. The participant's responses are collected and analysed qualitatively.

The finding that participants were ill prepared for adverse reactions, despite being warned of the possibility in the trial PIS, makes a compelling case for greater amounts of PPI in the development of future trials and research resources. During the TILT trial, a

dedicated MPM PPI group was established, and this group should be maintained and capitalised on for future studies, potentially using novel techniques such as “Meet the Researcher” that have been well-received in other patient research events in MPM (see Section 6.5.4.).(260)

Although the TwiC methodology was not feasible for use in future MPM trials, it may have a role in other respiratory illnesses. In order to shape and inform potential future trials, qualitative interviews with the research team and clinicians involved in TILT could provide useful information about the acceptability of this methodology to the people delivering the research. One observation of interest was that all ASSESS-meso participants who declined to be considered for TwiCs were enrolled at the same study site. Was the trial methodology explained in a different way at that centre? Or were the trial team less enthusiastic about the methodology and this was communicated to patients, either explicitly or sub-consciously? Given the novelty of the TwiC design and its potential use in other clinical settings, there is value in undertaking further work to delineate the acceptability and feasibility of its use as much as possible.

People with MPM were clear that the survival benefit offered by current treatment options were not sufficient to risk the adverse events associated with those treatments. To understand people with MPM’s decision-making and to help tailor future treatment offers, it would be interesting to investigate the relative importance of survival benefit against potential side effects using a discrete choice experiment (DCE). Initially designed by Kelvin Lancaster in relation to consumer choices in the field of economics, discrete

choice experiments present a series of hypothetical scenarios where single elements are altered sequentially to evaluate people's priorities and the level at which their decision changes.(349) In MPM, DCE could be used to determine what survival benefit chemotherapy would have to offer to make it acceptable or attractive to patients. Similarly, given the known side effect profiles of the newer immunotherapy agents, what level of clinical efficacy would people require before they contemplate receiving treatment? Do these decisions vary depending on patient characteristics, and if so, what are those characteristics? Further qualitative work could shed important light on these questions and help MPM clinicians and researchers understand patients' priorities and thus offer a more personalised approach to their care.

6.6. Conclusion

This thesis presents evidence about the role of intra-pleural bacterial immunotherapy in pleural malignancy, specifically MPM. Although intra-pleural bacterial agents have been studied as potential treatments for pleural malignancy for several decades, evidence for their anti-cancer activity is weak and beset by methodological issues. Bacteria arising in the pleural space due to pleural infection were not associated with improved survival in people with mesothelioma, in fact the opposite outcome was observed and people with pleural infection were more likely to die than those without. It was clear that randomised trial data was required to reliably determine the efficacy (or lack thereof) of intra-pleural bacteria in MPM.

The TILT trial was designed as a feasibility study of two intra-pleural bacterial agents, OK432 and BCG, based on the innovative, pragmatic TwiC methodology. TILT was the

first CTIMP to employ the TwiC design and demonstrated that the methodology could comply with the necessary clinical trial regulations and obtain the requisite approvals from the HRA and MHRA. Participants in TILT found the trial processes and methodological design acceptable, but ultimately the trial was unfeasible for several reasons. Recruitment was challenging due to a smaller eligible population than initially expected and the TwiC methodology added further restrictions to recruitment, for example the trial could not be advertised on clinical trial registers or patient support websites. Additionally, one of the fundamental premises of the TwiC approach, that control participants were unaware of the trial's existence, could not be maintained in people with MPM. Finally, attrition after randomisation occurred in both arms of the trial and this could have important implications for bias if a full-scale TwiC were planned. Both intra-pleural agents generated significant systemic inflammatory responses, and dose-reduction was necessary to attenuate this reaction.

Qualitative interviews revealed that people with MPM tended to be practical, stoical and well-informed about their disease and about research. Their desire for certainty in the face of an uncertain future created challenges in the communication of risk, which has potential implications for current clinical work and future research trials. People with MPM were motivated to participate in research by a combination of altruism and potential personal gain. In contrast, their relatives were more anxious about the future and felt protective of their family member and, as a result, were more reluctant for them to participate in research.

Effective treatment options are still required for MPM. Based on the findings of this thesis, a full-scale TwiC of intra-pleural OK432 or BCG in MPM is not recommended. However, future research approaches could involve embedding a traditional RCT within the ASSESS-meso cohort. This would facilitate more efficient recruitment and enable collection of long-term outcome data, whilst avoiding some of the challenges encountered by TILT. The work presented here will help inform future MPM trials and, hopefully, one day, contribute to the discovery of better treatment options for people with MPM.

List of papers published during the fellowship

In addition to the publications that arose directly from this thesis, listed on page iii, the following papers were published during the fellowship period, relating to work outside of my PhD. Authors contributions were confirmed at publication.

- Bibby AC, Blyth KG, Sterman DA & Scherpereel. Mesothelioma: is chemotherapy alone a thing of the past? In Maskell NA, Laursen CB, Lee YCG & Rahman NA (Eds). *ERS Monograph on Pleural Disease*. 1st Edition 2020, p 232-249.

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- Bibby AC & Maskell NA. Cough. *BMJ Online Learning Module*. 2016.

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Appendices

Appendix 1 – Search strategy for the systematic review

i) Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid Medline (R) Daily and Ovid Medline (R) <1946 to 2017 week 09>

1	malignant pleural effusion.mp. or exp Pleural Effusion, Malignant/	3988
2	malignant pleura$ effusion$.mp	2267
3	malignant pleura$ effusion$.m_titl	1191
4	pleural effusion.mp. or exp Pleural Effusion/	25996
5	(pleura* adj5 (effusion* or fluid*)).mp	30742
6	1 or 2 or 3 or 4 or 5	30742
7	exp Neoplasms/ or neoplas*.mp	3005820
8	(cancer* or tumor* or tumour* or carcinom* or malignan*).mp.	2896188
9	7 or 8	3778969
10	6 or 9	3795436
11	intra-pleura$.mp.	99
12	intra-pleura$.m_titl.	28
13	intra pleura$.mp.	99
14	intra pleura$.m_titl.	28
15	intrapleura$.mp.	2926
16	intrapleura$.m_titl	1209
17	11 or 12 or 13 or 14 or 15 or 16	2992
18	OK432.mp. or exp Picibanil/	1599
19	OK-432.mp.	1485
20	OK 432.mp.	1485
21	OK432.m_titl.	85
22	OK 432.m_titl.	849

23	OK-432.m_titl.	849
24	18 or 19 or 20 or 21 or 22 or 23	1880
25	corynebacterium parvum.mp. or exp Propionibacterium acnes/	3785
26	corynebacterium parvum.m_titl.	672
27	25 or 26	3785
28	BCG.mp. or exp Mycobacterium bovis/	31283
29	bacille calmette guerin.m_titl	653
30	28 or 29	31300
31	exp Adjuvants, Immunologic/ or exp Lactobacillus casei/ or LC9018.mp.	157064
32	superantigen.mp. or exp Superantigens/	5264
33	exp Superantigens/ or exp Bacterial Toxins/ or exp Staphylococcus aureus/ or exp Staphylococcal Infections/ or exp Lymphocyte Activation/ or staphylococ* superantigen.mp. or exp Enterotoxins/	348842
34	exp Staphylococcal Infections/ or superantigen.mp. or exp Streptococcus pyogenes/ or exp Staphylococcus aureus/ or exp Superantigens/ or exp Streptococcal Infections/	170762
35	exp Staphylococcus aureus/ or exp Bacterial Proteins/ or exp Membrane Proteins/ or exp Bacteria/ or exp Bacterial Infections/ or bacteri*.mp. or exp Bacterial Toxins/	3580177
36	Gram-Negative Aerobic Bacteria/ or Gram-Negative Bacteria/ or Gram-Negative Anaerobic Bacteria/ or Gram-Positive Endospore-Forming Bacteria/ or Bacteria, Anaerobic/ or Gram-Negative Chemolithotrophic Bacteria/ or Bacteria, Aerobic/ or Gram-Positive Bacteria/ or exp Bacteria/ or bacteria.mp. or Endospore-Forming Bacteria/	1304044
37	lipopolysaccharide.mp. or exp Lipopolysaccharides/	97434
38	Enterotoxin.mp or enterotoxin.m_titl	11746
39	immunotherapy.mp. or exp Immunotherapy, Active/ or exp Immunotherapy/ or exp Immunotherapy, Adoptive/	267316
40	coley.mp. or exp Cancer Vaccines/	11960
41	24 or 27 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40	3909247

42	10 and 17 and 41	404
43	limit 42 to human	316

Once duplicates removed – 312

ii) EMBASE via OVID <1974 to 2017 February 28>

1	malignant pleural effusion.mp. or exp Pleural Effusion, Malignant/	3991
2	malignant pleura$ effusion$.mp.	2267
3	malignant pleura$ effusion$.m_titl.	1191
4	(pleura* adj5 (effusion* or fluid*)).mp.	30749
5	pleural effusion.mp. or exp Pleural Effusion/	26003
6	1 or 2 or 3 or 4 or 5	30749
7	exp Neoplasms/ or neoplas*.mp.	3006214
8	(cancer* or tumor* or tumour* or carcinom* or malignan*).mp.	2897416
9	7 or 8	3780252
10	6 or 9	3796720
11	intra-pleura$.mp.	99
12	intra-pleura$.m_titl.	28
13	intra pleura$.mp.	99
14	intra pleura$.m_titl.	28
15	intrapleura$.mp.	2927
16	intrapleura$.m_titl.	1209
17	11 or 12 or 13 or 14 or 15 or 16	2993
18	OK432.mp. or exp Picibanil/	1599
19	OK-432.mp.	1485
20	OK 432.mp.	1485
21	OK432.m_titl.	85

22	OK 432.m_titl.	849
23	OK-432.m_titl.	849
24	18 or 19 or 20 or 21 or 22 or 23	1880
25	corynebacterium parvum.mp. or exp Propionibacterium acnes/	3786
26	corynebacterium parvum.m_titl.	672
27	25 or 26	3786
28	BCG.mp. or exp Mycobacterium bovis/	31289
29	bacille calmette guerin.m_titl.	653
30	(BCG or Mycobacterium bovis or bacille calmette guerin).m_titl.	12984
31	exp Adjuvants, Immunologic/ or exp Lactobacillus casei/ or LC9018.mp.	157068
32	superantigen.mp. or exp Superantigens/	5264
33	exp Superantigens/ or exp Bacterial Toxins/ or exp Staphylococcus aureus/ or exp Staphylococcal Infections/ or exp Lymphocyte Activation/ or staphylococ* superantigen.mp. or exp Enterotoxins/	348863
34	exp Staphylococcal Infections/ or superantigen.mp. or exp Streptococcus pyogenes/ or exp Staphylococcus aureus/ or exp Superantigens/ or exp Streptococcal Infections/	170782
35	exp Staphylococcus aureus/ or exp Bacterial Proteins/ or exp Membrane Proteins/ or exp Bacteria/ or exp Bacterial Infections/ or bacteri*.mp. or exp Bacterial Toxins/	3580690
36	Gram-Negative Aerobic Bacteria/ or Gram-Negative Bacteria/ or Gram-Negative Anaerobic Bacteria/ or Gram-Positive Endospore-Forming Bacteria/or Bacteria, Anaerobic/ or Gram-Negative Chemolithotrophic Bacteria/ or Bacteria, Aerobic/ or Gram-Positive Bacteria/ or exp Bacteria/ or bacteria.mp. or Endospore-Forming Bacteria/	1304276
37	lipopolysaccharide.mp. or exp Lipopolysaccharides/	97462
38	Enterotoxin.mp. or enterotoxin.m_titl.	11746
39	immunotherapy.mp. or exp Immunotherapy, Active/ or exp Immunotherapy/ or exp Immunotherapy, Adoptive/	267361
40	coley.mp. or exp Cancer Vaccines/	11960
41	24 or 27 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40	3908425

42	10 and 17 and 41	403
43	limit 42 to human	315

Once duplicates removed – 311
Removing duplication with MEDLINE search - 0

iii) Cochrane Central Register of Controlled Trials and Cochrane review database

#1	MeSH descriptor: [Pleural Effusion, Malignant] explode all trees	117
#2	malignant pleura* effusion*:ti,ab,kw (Word variations have been searched)	386
#3	#1 or #2	386
#4	MeSH descriptor: [Picibanil] explode all trees	94
#5	OK432 or OK-432 or OK 432:ti,ab,kw (Word variations have been searched)	146
#6	#4 or #5	159
#7	MeSH descriptor: [Propionibacterium acnes] explode all trees	104
#8	corynebacterium parvum:ti,ab,kw (Word variations have been searched)	99
#9	#7 or #8	154
#10	MeSH descriptor: [Mycobacterium bovis] explode all trees	84
#11	MeSH descriptor: [BCG Vaccine] explode all trees	745
#12	BCG or 'bacille calmette guerin':ti,ab,kw (Word variations have been searched)	1518
#13	#10 or #11 or #12	1531
#14	MeSH descriptor: [Bacteria] explode all trees	12403
#15	MeSH descriptor: [Bacterial Toxins] explode all trees	2115
#16	MeSH descriptor: [Superantigens] explode all trees	10
#17	MeSH descriptor: [Bacterial Proteins] explode all trees	1612
#18	MeSH descriptor: [Enterotoxins] explode all trees	120
#19	MeSH descriptor: [Membrane Proteins] explode all trees	15673
#20	MeSH descriptor: [Lipopolysaccharides] explode all trees	474

#21	MeSH descriptor: [Immunotherapy] explode all trees	7799
#22	MeSH descriptor: [Cancer Vaccines] explode all trees	279
#23	superantigen or enterotoxin or lipopolysaccharide or Coley:ti,ab,kw (Word variations have been searched)	982
#24	MeSH descriptor: [Adjuvants, Immunologic] explode all trees	1956
#25	MeSH descriptor: [Lactobacillus casei] explode all trees	143
#26	LC9018:ti,ab,kw (Word variations have been searched)	4
#27	#6 or #9 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26	39181
#28	#3 and #27	35

Removing duplicates with previous searches – 24 (16 excluded)

iv) US National Library of Medicine at www.Clinicaltrials.gov Searched on 01/03/2017

Search terms: "intra-pleural" and "malignant pleural effusion"

Study Type: all studies

Study Results: all studies

Recruitment: all studies

Eligibility Criteria: Adult (18–65) and Senior (66+)

21 results (all excluded)

v) International Standard Randomised Controlled Trial Number Registry at www.isrctn.com. Searched on 01/03/19.

Text search: blank

Condition: malignant pleural effusion

Interventions: blank

Funder Name: blank

8 results (all excluded, 1 duplicate)

vi) EU Clinical Trials Register www.clinicaltrialsregister.eu.
Searched 01/03/2017

1.	Malignant pleural effusion	122
2.	Intrapleural	15
3.	Intrapleural immunotherapy	0
4.	Malignant pleural effusion AND intrapleural	4
5.	Malignant pleural effusion AND immunotherapy	11
6.	Malignant pleural effusion AND bacteria	0
7.	Malignant pleural effusion AND OK432	0
8.	Malignant pleural effusion AND Corynebacterium parvum	0
9.	Malignant pleural effusion AND BCG	0
10.	Malignant pleural effusion AND lactobacillus casei	0
11.	Malignant pleural effusion AND Coley	0

TOTAL – 152 (all excluded)

vii) iSystem for Information on Grey Literature in Europe – SIGLE and the Open University Grey Literature site

Pleural	140
Intrapleural	4
Intra pleural	4
Intra-pleural	1
Pleural effusion	8
TOTAL	155 (all excluded)

Appendix 2 – Papers excluded from the systematic review at full-text stage and reasons for exclusion

Full-text article not available:

- Feixue SO, Xiaxia PE, Qimei JI, Yan PE, Jun ZH, Ji XI. Clinical effect of pseudomonas aeruginosa injection on malignant pleural effusion. Chinese Journal of Clinical Oncology. 2013:1127-9.
- Ikehara M, Oshita F, Suzuki R, Saitoh H, Yamada K, Noda K. Phase II study of OK-432 intrapleural administration followed by systemic cisplatin and gemcitabine for non-small cell lung cancer with pleuritis carcinomatosa. Journal of Experimental Therapeutics & Oncology. 2004;4(1).
- Wang J, Zhang H, Wang Y. Results of phase III clinical trial of Pseudomonas jinanensis vaccine injection (PVI) in the treatment of malignant pleural effusion. Zhonghua Zhong Liu Za Zhi [Chinese Journal of Oncology]. 1995;17(6):458-60.
- Fukuoka M, Takada M, Tamai S, Negoro S, Matsui K, Ryu S, Sakai N, Sakaguchi K. Local application of anti-cancer drugs for the treatment of malignant pleural and pericardial effusion. Gan To Kagaku Ryoho. Cancer & Chemotherapy. 1984;11(8):1543-9.
- Urata A, Nishimura M, Ota K. Randomized controlled study of OK-432 in the treatment of cancerous pleurisy. Gan To Kagaku Ryoho. Cancer & Chemotherapy. 1983;10(6):1497-503.

Survival outcomes not reported, or not reported separately for patients with MPE:

- Foresti V, Scolari N, Villa A, Parisio E, De Filippi G, Guareschi G. Malignant pleural effusions: meaning of pleural-fluid pH determination. Oncology. 1990;47(1):62-4.
- Kan N, Kodama H, Hori T, Takenaka A, Yasumura T, Kato H, Ogawa H, Mukaihara S, Kudo T, Ohsumi K, Mise K. Intrapleural adaptive immunotherapy for breast cancer patients with cytologically-confirmed malignant pleural effusions: an analysis of 67 patients in Kyoto and Shiga Prefecture, Japan. Breast cancer Research and Treatment. 1993;27(3):203-10.
- Ran ZA. Intracavitary infusion of Huachansu injection combined with polysaccharide nucleic acid fraction of Bacillus Calmette Guérin (BCG-PSN) or cisplatin in the treatment of malignant pleural and peritoneal effusions. Tumor. 2008;6:017.
- Salomaa ER, Pulkki K & Helenius H. Pleurodesis with doxycycline or Corynebacterium parvum in malignant pleural effusion. Acta Oncologica. 1995;34(1):117-121.
- Yasumoto K, Yamamura Y. Randomized clinical trial of non-specific immunotherapy with cell-wall skeleton of Nocardia rubra. Biomedicine & Pharmacotherapy. 1984;38(1):48-54.
- Yew WW, Chan SL, Kwan SY. Comparison of efficacy of mitomycin-C and corynebacterium parvum in the management of malignant pleural effusion. Chinese Medical Journal. 1988;101(10):737-9.

Duplicate publication of data

- Kan N, Kodama H, Hori T, Takenaka A, Yasumura T, Kato H, Ogawa H, Ohsumi K, Kudo N, Mukaihara S. Intrapleural treatment of breast cancer patients with pleural effusions: an analysis of 13 institutes in Kyoto and Shiga Prefectures. Kyoto and Shiga Breast Cancer Study Group. Gan to kagaku ryoho. Cancer & Chemotherapy. 1992;19(10 Suppl):1632-5.
- Yasumoto K, Ichinose Y, Yaita H, Tanaka K, Hara N, Ohta M, Hirota N, Nomoto K, Inokuchi K, Yamamura Y. Effect of adjuvant immunotherapy with Nocardia rubra cell-wall skeleton in lung cancer. Nihon Geka Gakkai Zasshi. 1983;84(4):321-7.

No participants with pleural effusions

- Holmes EC, Hill LD, Gail M. A randomized comparison of the effects of adjuvant therapy on resected stages II and III non-small cell carcinoma of the lung. The Lung Cancer Study Group. Annals of surgery. 1985;202(3):335.

Review article

- Miyanaga A, Gemma A. Pleuritis carcinomatosa. Gan To Kagaku Ryoho. Cancer & Chemotherapy. 2011;38(4):524-7.

Appendix 3 – Additional analyses from population-cohort study

Variable of interest	Interacting variable	P value*	Sensitivity analysis controlling for interacting variable		
			RR	95% CI	P value
Comorbidities	Age	0.018	1.17	1.13-1.20	<0.001
	IMD quintile	<0.001	1.17	1.13-1.20	<0.001
	Diagnosed after 2008	<0.001	1.19	1.15-1.22	<0.001
	No of pleural procedures	<0.001	1.19	1.16-1.23	<0.001
	No of hospital episodes per year	<0.001	1.20	1.16-1.23	<0.001
IMD quintile	Age	0.360	0.95	0.90-1.00	0.061
	Comorbidities	0.132	0.96	0.90-1.01	0.080
	Diagnosed after 2008	0.732	0.93	0.88-0.98	0.005
	No of pleural procedures	<0.001	0.92	0.87-0.98	0.006
	No of hospital episodes per year	0.053	0.96	0.91-1.02	0.180
No of pleural procedures	Age	0.056	1.54	1.46-1.63	<0.001
	Comorbidities	0.013	1.57	1.48-1.65	<0.001
	IMD quintile	0.269	1.61	1.52-1.70	<0.001
	Diagnosed after 2008	0.828	1.51	1.43-1.60	<0.001
	No of hospital episodes per year	<0.001	1.54	1.46-1.63	<0.001
Diagnosed after 2008	Age	0.043	1.03	0.86-1.23	0.765
	Comorbidities	0.016	0.95	0.80-1.14	0.595
	IMD quintile	0.650	1.11	0.93-1.32	0.250
	No of pleural procedures	0.355	1.03	0.86-1.23	0.757
	No of hospital episodes per year	0.190	1.02	0.99-1.04	0.186
No of hospital episodes per year	Age	0.190	1.02	0.99-1.04	0.186
	Comorbidities	0.021	1.01	0.98-1.03	0.681
	IMD quintile	0.868	0.99	0.97-1.02	0.558
	Diagnosed after 2008	0.827	1.01	0.99-1.03	0.465
	No of pleural procedures	0.006	1.00	0.98-1.02	0.774

Appendix Table 3a Mantel Haenszel test for interactions between pre-specified variables on the association with pleural infection

Abbreviations: CI – confidence interval, IMD – index of multiple deprivation, RR – relative risk

*chi^2 test for unequal RR

		Adjusted analysis		
		HR	95% CI	p
Pleural infection	Pre-infection/no infection	1	-	-
	First 30 days post- infection	1.88	1.51 to 2.36	<0.001
	30+ days post-infection	1.81	1.63 to 2.01	<0.001
Male gender		1.27	1.22 to 1.32	<0.001
Age at diagnosis	≤65	1	-	-
	66-70	1.17	1.12 to 1.23	<0.001
	71-75	1.33	1.27 to 1.39	<0.001
	76-80	1.57	1.50 to 1.65	<0.001
	≥81	1.86	1.78 to 1.95	<0.001
IMD quintile	1 (least deprived)	0.95	0.91 to 0.99	0.028
	2	0.94	0.90 to 0.98	0.007
	3	1	-	-
	4	0.96	0.92 to 1.01	0.111
	5 (most deprived)	1.00	0.95 to 1.04	0.852
	Missing	0.26	0.22 to 0.30	<0.001
Rural/urban location				
	Urban ≥10,000 population	1	-	-
	Town and Fringe	1.04	0.99 to 1.09	0.112
	Village	1.00	0.95 to 1.06	0.931
	Hamlet/ isolated dwelling	0.96	0.88 to 1.04	0.283
Mode of initial attendance				
	Outpatient appointment	1	-	-
	Hospital inpatient	1.14	1.04 to 1.25	0.007
	Operation/procedure	1.06	0.96 to 1.17	0.274
Diagnosed after 2008		0.87	0.85 to 0. 90	<0.001
No. of comorbid codes		0.97	0.97 to 0.98	<0.001
Non-pleural mesothelioma		0.94	0.91 to 0.96	<0.001
Documented asbestos exposure		1.10	1.06 to 1.15	<0.001
Documented pleural plaques		1.11	1.04 to 1.19	0.001
Pleural interventions				
	Pleural drainage/aspiration	1.22	1.17 to 1.27	<0.001
	Thoracoscopy	0.90	0.85 to 0.94	<0.001
	Percutaneous pleural biopsy	1.10	1.06 to 1.14	<0.001
	Pleurodesis	0.88	0.84 to 0.92	<0.001
Total no. of pleural procedures		0.87	0.85 to 0.89	<0.001
Average no. of hospital episodes per year		0.98	0.98 to 0.99	<0.001
Treatment received	Chemotherapy	0.99	0.95 to 1.02	0.475
	Radiotherapy	1.01	0.87 to 1.18	0.880
	Thoracic surgery	1.09	1.04 to 1.14	<0.001

Appendix Table 3b Factors associated with mesothelioma-specific mortality in 22,149 patients with mesothelioma, from adjusted Cox proportional hazards models. All listed variables were included in the multivariable model.

Abbreviations: CI – confidence interval; HR – Hazard ratio for mesothelioma-specific mortality; IMD – index of multiple deprivation.

		Adjusted analysis		
		HR	95% CI	p
Pleural infection				
	Pre-infection/no infection	1	-	-
	First 30 days post- infection	1.75	1.31 to 2.35	<0.001
	30+ days post-infection	1.86	1.64 to 2.11	<0.001
Male gender		1.29	1.23 to 1.36	<0.001
Age at diagnosis	≤65	1	-	-
	66-70	1.12	1.05 to 1.19	<0.001
	71-75	1.25	1.18 to 1.33	<0.001
	76-80	1.44	1.36 to 1.53	<0.001
	≥81	1.74	1.63 to 1.85	<0.001
IMD quintile	1 (least deprived)	0.92	0.86 to 0.98	0.008
	2	0.95	0.89 to 1.00	0.068
	3	1	-	-
	4	0.98	0.92 to 1.04	0.561
	5 (most deprived)	0.99	0.93 to 1.05	0.687
	Missing	0.27	0.22 to 0.32	<0.001
Rural/urban location				
	Urban ≥10,000 population	1	-	-
	Town and Fringe	1.03	0.97 to 1.10	0.303
	Village	1.03	0.96 to 1.11	0.350
	Hamlet/ isolated dwelling	0.94	0.84 to 1.05	0.306
Mode of initial attendance				
	Outpatient appointment	1	-	-
	Hospital inpatient	0.99	0.87 to 1.12	0.846
	Operation/procedure	0.93	0.81 to 1.05	0.244
Diagnosed after 2008		0.87	0.84 to 0.91	<0.001
No. of comorbid codes		0.99	0.98 to 0.99	0.005
Documented asbestos exposure		1.07	1.02 to 1.13	0.004
Documented pleural plaques		1.10	1.02 to 1.20	0.016
Pleural interventions				
	Pleural drainage/aspiration	1.13	1.07 to 1.19	<0.001
	Thoracoscopy	0.85	0.80 to 0.90	<0.001
	Percutaneous pleural biopsy	1.05	1.01 to 1.10	0.029
	Pleurodesis	0.84	0.80 to 0.89	<0.001
Total no. of pleural procedures		0.91	0.88 to 0.93	<0.001
Average no. of hospital episodes per year		0.99	0.98 to 0.99	<0.001
Treatment received	Chemotherapy	0.54	0.51 to 0.57	<0.001
	Radiotherapy	0.92	0.74 to 1.13	0.415
	Thoracic surgery	0.85	0.80 to 0.90	<0.001

Appendix Table 3c Factors associated with all-cause mortality in 11,401 patients with pleural mesothelioma, from adjusted Cox proportional hazards models, in which all listed variables were included.

Abbreviations: CI – confidence interval; HR – Hazard ratio for mortality; IMD – index of multiple deprivation.

Variable	VIF	Tolerance	R^2
Pleural infection	1.08	0.926	0.074
Male gender	1.03	0.968	0.032
Age at diagnosis	1.20	0.830	0.169
IMD quintile	1.04	0.964	0.036
Rural/urban location	1.03	0.972	0.028
Mode of initial attendance	1.10	0.907	0.093
Diagnosed after 2008	1.10	0.905	0.095
No. of comorbid codes	1.22	0.817	0.182
Non-pleural mesothelioma	1.08	0.927	0.073
Documented asbestos exposure	1.08	0.926	0.075
Documented pleural plaques	1.04	0.966	0.034
Pleural interventions			
Pleural drainage/aspiration	1.83	0.547	0.453
Thoracoscopy	2.72	0.367	0.633
Percutaneous pleural biopsy	1.23	0.812	0.189
Pleurodesis	1.95	0.514	0.486
Total no. of pleural procedures	4.57	0.219	0.781
Average no. of hospital episodes per year	1.11	0.898	0.102
Treatment received			
Chemotherapy	1.14	0.878	0.121
Radiotherapy	1.00	0.996	0.004
Thoracic surgery	1.43	0.701	0.299

Appendix Table 3d Test for collinearity within multivariable survival analysis.

Abbreviations: IMD – index of multiple deprivation, VIF - variance inflation factors.

Appendix 4 – Case Report Forms from the ASSESS-meso and TILT studies

Participant study ID		Participant initials		Date of completion	DD	MM	YYYY

CLINICAL ASSESSMENT (BASELINE)

1. TILT ELIGIBILITY & PARTICIPATION

Have you assessed the participant's eligibility for TILT?	YES	NO
Are they eligible to participate in TILT?	YES	NO

If you have not assessed their eligibility for TILT, please do so, using form TILT01 or the trial database.
If the participant is eligible for TILT, please complete data collection for this visit, and refer to the TILT protocol for instructions on what to do next.

2. PARTICIPANT INFORMATION

Sex				MALE	FEMALE
Age					years
Weight					kgs
Height					m
Performance status	0	1	2	3	4

Date diagnosis of MPM was confirmed at MDT			DD/MM/YYYY	
Method of diagnosis	Clinico-radiological		Cytology	Histology
If 'Histology', what was the diagnosis?	Epithelioid	Sarcomatoid	Biphasic	Desmoplastic
If 'Histology', how was it obtained?	Ultrasound biopsy	CT guided biopsy	Medical thoracoscopy	Surgical thoracoscopy
Side of disease		Bilateral	Left	Right
IPC in situ?			YES	NO
Date of IPC insertion			DD/MM/YYYY	
Side of IPC		Bilateral	Left	Right

Participant study ID		Participant initials			Date of completion	DD	MM	YYYY

3. SYMPTOMS

What symptoms did the participant have at presentation? (Tick all that apply)			
Chest pain			
Breathlessness			
Cough			
Fevers/sweats			
Fatigue/lethargy			
Anorexia			
Weight loss			
Other (please specify:_____)			
Duration of symptoms at presentation	<1 month	1-2 months	> 2 months

4. PREVIOUS MEDICAL HISTORY

Does the participant have a history of any of the following conditions?

CANCER		
Previous or current malignancy (other than MPM)	YES	NO
Previous or current?	Previous	Current
What malignancy?		
RESPIRATORY DISEASE Asthma/COPD	YES	NO
Interstitial lung disease (ILD)	YES	NO
Bronchiectasis	YES	NO
Pulmonary hypertension	YES	NO
Pulmonary emboli/ DVT	YES	NO
Pleural infection	YES	NO
(If yes, which side?)	Left	Right
Other respiratory condition (specify:_____)	YES	NO
CARDIAC DISEASE Ischaemic heart disease	YES	NO
Atrial fibrillation	YES	NO
Heart failure	YES	NO
Valvular disease	YES	NO

Participant study ID		Participant initials		Date of completion	DD	MM	YYYY

Other cardiac condition (specify: _____)		YES	NO
OTHER SIGNIFICANT CONDITION	Diabetes	YES	NO
	(If yes, are you on insulin?)	YES	NO
	Chronic kidney disease	YES	NO
Gastrointestinal condition (specify:_____)		YES	NO
Neurological condition (specify:_____)		YES	NO
Endocrine/hormone condition (specify:_____)		YES	NO

5. PREVIOUS PLEURAL INTERVENTIONS

Procedure	Undertaken?		No of times performed
Diagnostic tap	YES	NO	
Therapeutic aspiration	YES	NO	
Chest drain (excluding post-thoracoscopy drains)	YES	NO	
Talc slurry pleurodesis	YES	NO	
Image-guided percutaneous pleural biopsy	YES	NO	
Local anaesthetic thoracoscopy	YES	NO	
Surgical thoracoscopy or other surgical procedure	YES	NO	
Talc poudrage	YES	NO	
Intra-pleural fibrinolytics	YES	NO	
Other (please specify)_____	YES	NO	

Please complete the boxes below for each pleural procedure.

If they have not had any previous pleural procedures, go to Section 6.

DIAGNOSTIC TAP			
What date was the diagnostic tap?	DD	MM	YYYY
Which side was the diagnostic tap?	Left		Right
What was the pleural fluid LDH?			U/L
What was the pleural fluid total protein?			g/L
What was the pleural fluid glucose?			mmol/L
What was the serum LDH?			U/L
What was the serum total protein			g/L

Participant study ID		Participant initials		Date of completion	DD	MM	YYYY

What was the predominant cell type on the first tap?	

THERAPEUTIC ASPIRATION			
What date was the therapeutic aspiration?	DD	MM	YYYY
Which side was the therapeutic aspiration?	Left		Right
What was the volume aspirated?			mls

CHEST DRAIN (excluding post thoracoscopy drains)			
What date was chest drain inserted?	DD	MM	YYYY
Which side was the chest drain?	Left		Right
What was the total volume drained?			mls

TALC SLURRY PLEURODESIS			
What date was the talc slurry pleurodesis?	DD	MM	YYYY
Which side was the talc slurry pleurodesis	Left		Right

IMAGE GUIDED PERCUTANEOUS BIOPSY			
What date was the biopsy?	DD	MM	YYYY
Which side was the biopsy?	Left		Right

LOCAL ANAESTHETIC THORACOSCOPY			
What date was the thoracoscopy?	DD	MM	YYYY
Which side was the thoracoscopy?	Left		Right

SURGICAL PROCEDURE			
What was the surgical procedure?			
What date was the surgical procedure?	DD	MM	YYYY
Which side was the surgical procedure?	Left		Right

TALC POUDRAGE			
What date was the talc poudrage?	DD	MM	YYYY
Which side was the talc pleurodesis?	Left		Right

INSERTION OF AN INDWELLING PLEURAL CATHETER			
What date was the IPC inserted?	DD	MM	YYYY
Which side was the IPC?	Left		Right

Participant study ID		Participant initials		Date of completion	DD	MM	YYYY

REMOVAL OF AN INDWELLING PLEURAL CATHETER				
What date was the IPC removed?		DD	MM	YYYY
Why was the IPC removed?	Infected IPC	Blocked IPC	Auto-pleurodesed	Not draining as loculated
	Damaged IPC	Other (specify):		

INTRAPLEURAL FIBRINOLYTICS		
Which intrapleural fibrinolytics (circle all that apply)	TpA	DNAse
	Streptokinase	Urokinase
	Other:_____	
What was the start date for the intrapleural fibrinolytics?	DD	MM YYYY
How many doses were given in total?		

Were any of the above procedures felt to be necessary but not carried out, or attempted but not completed?	YES	NO

(e.g. Patient required therapeutic aspiration, but procedure not undertaken as patient anticoagulated). If yes, please provide details below. If no, go to Section 6.

Procedure	Date			Reason not undertaken or completed
	DD	MM	YYYY	
	DD	MM	YYYY	

Participant study ID		**Participant initials**			**Date of completion**	DD	MM	YYYY

6. PLEURAL DRAINAGE

If the participant has an IPC in situ, please complete the table below with the date and volume of every drainage in the past 4 weeks, or since the IPC was inserted if less than 4 weeks (including today's drainage). If the participant does not have an IPC in situ, please go to Section 7.

Date			**Volume drained (mls)**
DD	MM	YYYY	
DD	MM	YYYY	
DD	MM	YYYY	
DD	MM	YYYY	
DD	MM	YYYY	
DD	MM	YYYY	
DD	MM	YYYY	
DD	MM	YYYY	
DD	MM	YYYY	
DD	MM	YYYY	

Date			**Volume drained (mls)**
DD	MM	YYYY	
DD	MM	YYYY	
DD	MM	YYYY	
DD	MM	YYYY	
DD	MM	YYYY	
DD	MM	YYYY	
DD	MM	YYYY	
DD	MM	YYYY	
DD	MM	YYYY	
DD	MM	YYYY	

7. PREVIOUS MESOTHELIOMA TREATMENT

Treatment	Received ?		Please provide details		No of cycles	Date first cycle started	Date final cycle ended
Chemotherapy	YES	NO	What regimen?			(DD/MM/YY)	(DD/MM/YY)
Radiotherapy	YES	NO	Prophylactic	Palliative			
Surgery	YES	NO	What operation?		**X**		
Bevacizumab	YES	NO					
Trial medication	YES	NO	What trial?				
Other	YES	NO					

Participant study ID		**Participant initials**		**Date of completion**	DD	MM	YYYY

Has the patient chosen not to receive a specific treatment at any point?	YES	NO
If yes, what treatment did they chose not to receive?		
What were their reasons for choosing not to have it?		

8. MEDICATION HISTORY

Please list all medications that the participant is currently taking:

Drug (generic name in CAPITALS)	**Dose** (inc units, e.g. 10mg)	**Route** (po/sc/im/iv/ng/ pr/patch)	**Regular or PRN?**	**Frequency** (Doses per day - if PRN give approx. frequency)

Participant study ID		**Participant initials**		**Date of completion**	DD	MM	YYYY

CHECKLIST	DONE
Please uploaded this data onto the study database.	
Please complete eCRF AM08 'Blood tests' for this visit.	
Please complete eCRF AM09 'Imaging' for this visit.	
Have you asked the participant to complete an EQ-5D-5L QoL questionnaire (eCRF AM10) for this visit?	
Have you asked the participant to complete symptom VAS scores (eCRF AM11) for this visit?	
Does participant have a date for their next trial visit? (nb this should correspond with their next clinic appointment, if within 3 months)	
If the participant is eligible for TILT, they are now ready for randomisation. Please log on to REDCAP & complete eCRF TILT-07a - Randomisation	

If the participant is eligible for TILT, please complete the checklist below:

Please randomise the participant using the randomisation module in REDCAP. You may wish to use cribsheet TILT-07a to collect the data for randomisation. **DO NOT INFORM PARTICIPANT ABOUT RANDOMISATION AT THIS STAGE**	
Provide participant with VAS booklet (AM12)	
Please arrange next trial visit appointment	

		DD	MM	YYYY
Researcher completing form	**Signature**	**Date**		

This checklist is intended to assist with data entry onto the electronic CRF. Once completed, this checklist can be stored in the patient's notes as source data, stored securely in the participant's trial file or destroyed.

Participant study ID		Participant initials		Date of completion	DD	MM	YYYY

BLOOD TESTS

9. BLOOD TESTS

	Result	Date
Haemoglobin (g/dL)		
WCC (x10^9/L)		
Neutrophils (x10^9/L)		
Lymphocytes (x10^9/L)		
Platelets (x10^9/L)		

	Result	Date
Sodium (mmol/L)		
Potassium (mmol/L)		
Urea (mmol/L)		
Creatinine (mmol/L)		
eGFR (mL/min/1.73M^2)		

CRP (mg/L)			
INR			
Albumin (g/L)			
Serum mesothelin			

Bilirubin (µmol/L)				
AST (U/L)				
ALT (U/L)				
Alk phos (U/L)				

		DD	MM	YYYY
Researcher's name (PRINT)	**Signature**	**Date**		

Participant study ID		Participant initials		Date of completion	DD	MM	YYYY

IMAGING

1. CHEST X-RAY

Did the participant have a chest x-ray today?	YES	NO
If not, why not? (please tick one)	Participant declined	
	Not clinically indicated	
	Participant too frail	
	Other	

Is the x-ray normal?	YES	NO
If not normal, which side are the abnormalities?	LEFT	RIGHT
What are the abnormalities? (Tick all that apply)	Pleural plaques	
	Pleural thickening	
	Pleural opacification/ fluid covering < 25% of the hemithorax	
	Pleural opacification/ fluid covering 25-50% of the hemithorax	
	Pleural opacification/ fluid covering >50% of the hemithorax	
	Loculated pleural effusion	
	Hydropneumothorax/ trapped lung with < 50% pleural apposition	
	Hydropneumothorax/ trapped lung with >50% pleural apposition	
	Other abnormality (please specify:_____)	

2. CT THORAX

Has the participant had a CT chest since their last assessment?	YES	NO
What was the date of their last CT chest?	DD MM YYYY	
What is the radiological staging on the most recent CT scan?	**T** **N** **M**	
What is the disease status on the most recent CT scan?	Disease progression	
	Stable disease	
	Partial response	
	Complete response	
	Not applicable (this is 1st scan)	

Participant study ID		Participant initials			Date of completion	DD	MM	YYYY

3. THORACIC USS - To be completed only if the participant has a pleural effusion.

Which side is the effusion	BILATERAL	LEFT	RIGHT
Was thoracic ultrasound performed today?		YES	NO

If not, why not? (please tick one)	
Participant declined	
Not clinically indicated	
Participant too frail	
Other (please specify:_____)	

Please grade the degree of septation/loculation for the effusion. If the participant has bilateral effusions, please grade the effusions separately by writing L or R in the relevent box.

	Free-flowing: Non-loculated, no visible septations	
	Mild: Non-loculated, up to 3 septations visible at maximally septated area	
	Moderate: Fluid separated into locules. Between 4 and 9 septations visible at maximally septated area	
	Heavy: Fluid separated into locules. More than 10 septations visible at maximally septated area	

		DD	MM	YYYY
Researcher completing form	**Signature**	**Date**		

EQ-5D-5L Quality of life questionnaire

Participant study ID		Participant initials		Date of completion	DD	MM	YYYY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

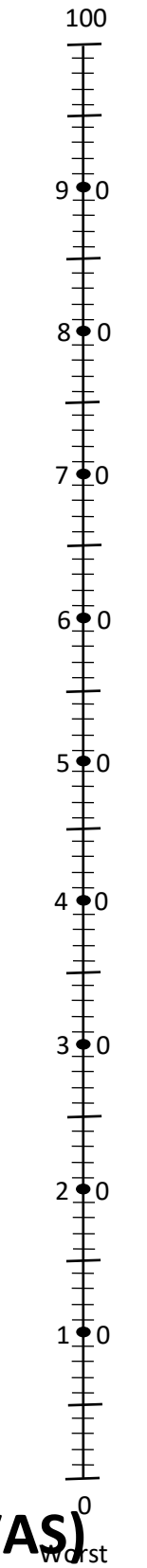
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

Participant study ID		Participant initials		Date of completion	DD	MM	YYYY

VISUAL ANALOGUE SCALES (VAS)

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.



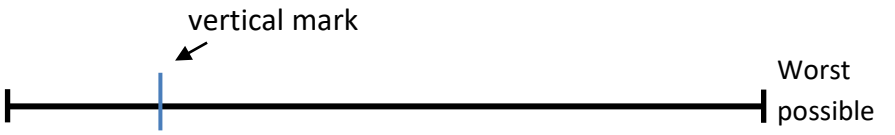
YOUR HEALTH TODAY =

Participant study ID		Participant initials		Date of completion	DD	MM	YYYY

Visit No.

Please place a single vertical mark on each line to show how severe your symptoms have been in the past 24 hours. An example is shown below, but if you are unsure, please ask a member of the research team to help you.

EXAMPLE:

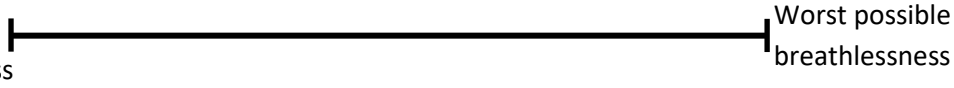


IN THE PAST 24 HOURS

HOW MUCH CHEST PAIN HAVE YOU EXPERIENCED?

IN THE PAST 24 HOURS

HOW BREATHLESS HAVE YOU FELT?



IN THE PAST 24 HOURS

HOW MUCH SWEATING HAVE YOU EXPERIENCED?

Thank you!

Appendix 5 – Qualitative interview invitation letter to bereaved relatives

NHS
North Bristol
NHS Trust

Clinical Research Centre - Respiratory
Southmead Hospital
Westbury on Trym
Bristol BS10 5NB

Tel: 0117 414 8114 | Fax: 0117 414 8149
Email: respiratoryresearch@nbt.nhs.uk
Web: www.nbt.nhs.uk

TILT
ASSESS-meso

Date

Dear [insert name]

I am writing to express my sincere sympathy following the sad loss of your husband/ wife.

I also wanted to tell you how grateful I am for _____'s involvement in our research. I recognise that taking part made demands of both of your time and energy, and I wanted to let you know that those efforts were appreciated.

_____'s experience of taking part in research is important to us, as is your experience of helping him/her take part. If you, or a member of your family, wanted to share your thoughts about _____'s involvement in research, we would be very interested to hear about it, in a face-to-face meeting. I have included an information sheet with this letter so you can read about what that meeting would involve. If you would like me to give you a call and tell you a bit more about it, please return the enclosed form with your telephone number and the best time of day to call.

If you do not want to do this, I completely understand, and **we will not contact you about it again**. I would like to thank you once more for _____'s and your contribution to our research and let you know that my thoughts are with you at this difficult time.

With best wishes,

[redacted]

Dr Anna Bibby
Pleural Research Fellow

Date_____

Dear Dr Bibby

Re: Invitation to take part in a one-to-one interview

I am considering meeting to talk about my relative's participation in research and/or I am interested in hearing more about what it would involve. I would like to be contacted by a member of the research team to discuss it in greater detail.

Name:_____

Telephone
number:_____

Mobile phone
number:_____

Best time(s) of day to
telephone:_____

_____ _____

(Signature) (Date)

Appendix 6 – Topic guide for qualitative interviews

Interview topic guide

The interviewer will use this guide as a flexible template for interview topics and questions. However the interviewer will also respond to participants' answers and statements, and will explore other topics if and when they arise.

Introduction

Explain that the interview will be recorded and discuss issues of confidentiality and anonymisation. Explain that the aim of the research is to understand participants' experiences of having mesothelioma and taking part in a research study. The information will be used to improve future research studies, and our interactions with patients in clinical care.

Reaffirm consent, and check that the participant is happy to take part in the interview. Check whether the participant has any questions prior to starting the interview.

Part 1 – participating in research

I'd like to talk about your participation in research.

- Overall experience of pleural service
- Initial thoughts on ASSESS-meso
- Factors affecting decision to take part
- Discussed with anyone?
  - Who and what?
- Did potential for trials affect decision?
  - Positive or negative? Agree to be considered for future trials?
- ASSESS-meso assessments
  - Frequency
  - Ease of completion
  - Blood tests & IPC drainages
- Anything particularly good?
- Anything particularly difficult?

Part 2 – receiving OK-432/BCG (for TILT participants only)

- Initial invitation to join TILT
- Thoughts, feelings or concerns about OK-432/BCG
- Experience receiving OK-432/BCG
- Any problems after OK-432/BCG?
- Future trial participation

Part 3 – reasons for not participating (people who declined any element of the study)

- Reasons for not participating
- Anything that would have changed your decision?
- Any other considerations?

Part 4 – TWIC methodology

- Explain RCT design – any thoughts?
- Explain TWICS – what thoughts?
- More or less fair?
- How would you feel if you found out other people in ASSESS-meso had been invited to join a trial and you had not?

Thank you and close

- Any other thoughts about research?
- Any other comments about mesothelioma?
- Any questions for me?

Thank you for taking part.